Evaluation of the effect of pharmacological treatment on cognition in patients with bipolar disorder 1- A prospective observational study

Thesis submitted to

the faculty of

ALL INDIA INSTITUTE OF MEDICAL SCIENCES, BHOPAL

For the award of the degree of MD in the subject of

Pharmacology

by

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(October 2023)

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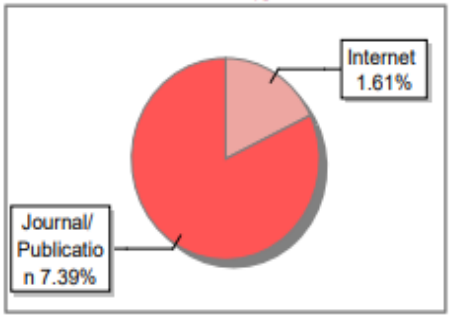

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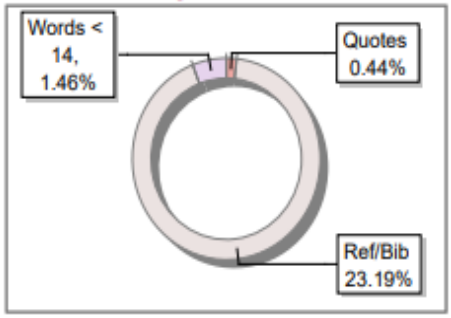

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List of Abbreviations:

AE	**Adverse event**
ADR	**Adverse drug reaction**
ALDH2	**Aldehyde dehydrogenase 2**
APA	**American psychiatric association**
AUC	**Area under curve**
BPD	**Bipolar disorder**
BDNF	**Brain derived neurotrophic factor**
CACNA1C	**Calcium voltage gated channel subunit alpha1 C**
CBT	**Cognitive behavioural therapy**
CHRNA7	**Cholinergic receptor nicotinic alpha 7 subunit**
COBRA	**Cognitive complaints in bipolar disorder rating assessment**
CPGs	**Clinical practice guidelines**
DALY	**Disability adjusted life years**
DSM	**Diagnostic and Statistical Manual of mood disorders**
ECT	**Electroconvulsive therapy**
GABA	**Gamma amino butyric acid**
HAMD	**Hamilton depression rating scale**
ICC	**Intraclass coefficient**
ICD	**International Classification of Diseases**
ICH-GCP	**International Council of Harmonisation-Good Clinical Practice**
IPS	**Indian Psychiatric Society**
IQR	**Inter quartile range**
MAPK1	**Mitogen activated protein kinase 1**
MARS	**Medication adherence rating scale**
MoCA	**Montreal cognitive assessment scale**
MRI	**Magnetic resonance imaging**
MsRA	**Methionine sulfoxide reductase A**
NICE	**National institute of Health and Care Excellence**
OPD	**Out Patient Department**
QOL	**Quality of Life**
ROC	**Receiver operating curve**
SD	**Standard deviation**
SNP	**Single nucleotide polymorphism**
TCA	**Tricyclic antidepressant**
T2DM	**Type 2 diabetes mellitus**
YLD	**Years lost to disability**

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INTRODUCTION

INTRODUCTION

Bipolar disorder is a chronic, debilitating mood disorder affecting 40 million people worldwide and forms a significant cause of disability. [1] Total lifetime (and 12-month) prevalence estimates for bipolar disorder I, bipolar disorder II, and subthreshold bipolar disorder were 2.4% (1.5%) according to the World Mental Health Survey Initiative. [2]According to the Golden burden study, the prevalence of bipolar disorders, in India was 0.6% (0.5-0.7). [3]

People with bipolar disorder endure significant impairment and are symptomatic for roughly half of their lives with syndromal or subsyndromal symptoms, mainly those of depression. Patients are unable to perform their jobs properly. Both symptomatic and non-symptomatic patients experience decreased quality of life, and patients have noted that several functional domains are involved, including physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, and education. Suicide is one of the primary causes of death in bipolar disorder. Clinicians must regularly check on their patients to observe the danger and ideation of suicide. With 6%–7% of bipolar disorder patients who have been identified committing suicide, bipolar disorder has a far greater suicide risk than the general population (10.7 per 100 000 per year). [2]

Bipolar disease is the 16th leading cause of years lost to disability (YLD) worldwide, according to the Global Burden of Disease Study, accounting for 9.9 million YLD. Since bipolar disorder is the 6th -leading cause of disability-adjusted life years among people aged 10 to 24 years worldwide, its effects on young people are considerably more profound. [2]

14.5 % of all years lost to disability in India in 2017 were primarily caused by mental disorders. In India, these were the main factor in 14.5 % of all years lost to disability in

2017. According to estimates, bipolar disorder contributed 6.9% (4.9%–9.6%) of all DALYs. [3]

The Diagnostic and Statistical Manual of Mental Disorders (DSM) and the International Classification of Diseases (ICD) of the World Health Organisation (WHO) are the two principal classifications used in psychiatry. [4]

A manic episode is a defining feature of bipolar disorder type 1. A hypomanic or significant depressed episode may come before or after the manic phase.[5] The full criteria for mania are absent in some bipolar individuals (bipolar disorder-2), and the requisite recurring depressions are rather separated by periods of modest activation and raised energy (hypomania). In cyclothymic disorder, there are a lot of hypomanic episodes, usually of short duration, that are interspersed with depressive symptom clusters that do not fulfil the standards for major depression in terms of intensity or duration. Before a diagnosis can be made, the chronic mood swings must last for at least two years. Manic episodes generally begin over days to weeks, although they can occasionally start suddenly and last only a few hours., occurring usually in the early morning hours. Patients who experience four or more episodes of mania or depression in a year are said to be rapid cycling. 15% of patients have this pattern, primarily in female patients. [6]

The depressive phase, rather than the mania itself, are more responsible for deterioration in work performance and psychosocial functioning, which affects about half of patients. Although this onset usually occurs between the ages of 20 and 30, numerous individuals describe premorbid symptoms as early as late childhood or early adolescence. Similar rates of prevalence are seen in both males and women. [6]

Initial hypotheses on the aetiology of bipolar disorder focused mainly on the system of neurotransmission of biogenic amines. There is not a single theory explaining bipolar disorder's genetic, biochemical, pharmacological, anatomical, and sleep data. For transmitters (catecholamines, serotonin, gamma aminobutyric acid (GABA), glutamate, and others), hormones (brain-derived neurotrophic factor, thyroid, and others), and steroids-alone and in combination-biochemical studies are currently being studied. [7]

One major component of this disability is cognitive impairment, a broad term that refers to deficits in the mental action or process of acquiring knowledge and understanding through thought, experience, and senses. This issue has received considerable critical attention in recent decades as patients with bipolar disorder are found to have cognitive deficits regardless of their phase of illness. In manic, depressive, and mixed states, findings consistently show significant impairment in the domains of verbal memory, attention, language, and executive function. In euthymic patients, the presence and extent of cognitive deficits is more varied. It is estimated that among patients of bipolar disorder, 29–48% show no impairment, 12–40% display specific impairments in verbal learning, working memory and executive function, and 12–40% have impaired cognition in all domains. [8]

The underlying causes of cognitive impairment in bipolar disorder patients are still not fully understood. Numerous research has shown that the causes of cognitive impairment among individuals with bipolar disorder are complex and include gene polymorphism, changes in brain structure and function, as well as inflammatory and metabolic factors. [9]

Several guidelines have been created to assist clinicians in making appropriate treatment decisions in order to ensure individuals with the condition receive evidence-based care American Psychiatric Association (APA), 2020; National Institute for Health Clinical

Excellence (NICE), 2014; and the most recent Canadian Network for Mood and Anxiety Treatments/International Society for Bipolar Disorders. These guidelines have been developed considering the complexity of treating bipolar disorder. Most Indian physicians (85%) admitted using APA guidelines, then Indian Psychiatric Guidelines, or IPS, (75%), followed by other standards. [10]

It is well-known that there is a steady correlation between a person's cognitive ability and their social and occupational function. In addition to their early onset, bipolar disorder is also characterised by a high prevalence and severity of cognitive impairment. Clinical management needs to concentrate on the assessment of cognition and the impact of these changes on quality of life due to the high prevalence and extent of cognitive impairment in bipolar disorder, the early onset of these deficits, and their detrimental impact on the psychosocial and professional development of individuals. The cognitive adverse effects of medication should also be considered since pharmacological interventions make up a substantial part of management of bipolar disorder. [8]

According to Indian Psychiatric Society's Clinical Practice Guidelines, mood stabilisers, antidepressants, antipsychotic medications, electroconvulsive therapy (ECT), adjunctive medications, and psychosocial interventions can all be used as treatment options for bipolar disorder. Mood stabilisers are the cornerstone of bipolar disorder treatment. Lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine, and topiramate are some of the mood stabilisers that are available. [11]

There are not many studies concerning the effect of pharmacological treatment, so it's still unclear how does it affect the cognition. Additionally, it has been seen that some of the drugs utilised can have a favourable or negative impact on a patient's cognitive function. [12] Particularly, it has been seen that the use of atypical antipsychotics in case of acute illness has been linked to cognitive improvement in bipolar disorder. The

atypical antipsychotic clozapine has been studied the most and has been linked to slight increases in verbal fluency and motor speed. Improvements in verbal learning and memory, verbal fluency, and executive function have been linked to olanzapine, a similar drug. [13] It appears that risperidone improves verbal and working memory, motor skills, emotional perception, selective attention, and long-term memory. [14] Some studies suggest on administration of quetiapine there is a significant improvement in verbal memory, attention, executive function, verbal reasoning, fluency skills and visuomotor tracking. [15] In regards to mood stabilizing agents, patients treated with lithium had better preserved attention, memory, and most executive functions in comparison to other mood stabilizing agents, although this has not been a consistent finding in all the studies. [8]

REVIEW OF LITERATURE

REVIEW OF LITERATURE

History of bipolar disorder:

The first description of symptoms of depression and mania were analysed in the first century B.C. in Greece by a man by the name of Aretaeus of Cappadocia. There is documentation that demonstrates how bath salts were used to help those with depression and to calm individuals with manic episodes. Very little research or discovery occurred over the centuries. [16]

Hippocrates (460–370 B.C.), a physician in ancient Greece who is regarded as "the father of medicine," is responsible for the earliest references to bipolar illness in medical history. He was the first to describe two extreme states of mind: being excessively down (what we now refer to as depression) and being extraordinarily ecstatic or joyful (mania). Melancholia was Hippocrates' term for the condition of profound grief. The phrase translates to "black bile" since "melas" was a synonym for "black" and "chole" was a synonym for "bile." On the other hand, mania was thought to be due to an excess of yellow bile. [16]

Aretaeus of Cappadocia, a first-century Greek physician, is credited with being the first to articulate the idea of a mood spectrum with these extreme emotions on either end. He was also the first to discover that mania and melancholia were linked to a brain disorder. [16]

In his writings, the Athenian philosopher Plato (428–348 B.C.) explored the idea of insanity and distinguished between two types: "one involving a mental strain that arises from a bodily cause of origin, the other divine or inspired." Being able to discern between

the two, Hippocrates and Aretaeus each attempted to establish that melancholia and mania were biological disorders and not only psychological responses to a situation. [17]

The earliest known diagnosis of bipolar illness is thought to have been made by a French psychiatrist by the name of Jean-Pierre Falret in an article describing "circular insanity" in the middle of the 19th century. Years later, in the early 1900s, a German psychiatrist named Emil Kraepelin examined the impact of biology on mental diseases like bipolar disorder. His research continues to serve as the foundation for categorising mental illnesses today. [17]

Meanwhile, Karl Kahlbaum (1828–1899), a German psychiatrist, divided mental diseases into two categories: those that caused only a slight disruption of the mind and those that caused a complete disturbance of the mind. [17]

By the turn of the century, manic-depressive insanity, which was coined by another German psychiatrist known as the father of modern psychiatry, Emil Kraepelin (1856–1926), combined all forms of affective illnesses. And despite some resistance, Kraepelin's theory was accepted—at least temporarily. [17]

Carl Gustav Jung introduced the first diagnostic differentiation between manic-depression involving psychotic symptoms and that which does not in 1903. In the DSM-IV, Jung's distinction between "bipolar I" (mania with the potential for psychotic episodes) and "bipolar II" (hypomania without psychosis) is now known. [16]

Epidemiology:

Total lifetime (and 12-month) prevalence estimates for bipolar disorder I, bipolar disorder II, and subthreshold bipolar disorder were 2.4% (1.5%) according to the World Mental Health Survey Initiative. [2] According to the Golden burden study, the prevalence of bipolar disorders, in India was 0.6% (0.5-0.7). [3]

With a 25-year average start age, bipolar disorder typically appears in late adolescence and early adulthood. These can be classified into a large early onset group (mean ± standard deviation (17.24 ± 3.20 years), and smaller middle-onset (23.93 ± 5.12 years) and late-onset (32.20 ± 11.96 years) groups. The proportion of people falling into each category is 41.7%, 24.7%, and 33.6% of the total sample, respectively. Statistical models suggest the existence of three age of onset subgroups within bipolar disorder 1. [2]

Bipolar disease is the 16th leading cause of years lost to disability (YLD) worldwide, according to the Global Burden of Disease Study, accounting for 9.9 million YLD. Since bipolar disorder is the 6th -leading cause of disability-adjusted life years among people aged 10 to 24 years worldwide, its effects on young people are considerably more profound. [2]

14.5 % of all years lost to disability in India in 2017 were primarily caused by mental disorders. In India, these were the main factor in 14.5 % of all years lost to disability in 2017. According to estimates, bipolar disorder contributed 6.9% (4.9%–9.6%) of all DALYs. [3]

Diagnostic assessment:

Bipolar disorder comprises of a spectrum of diagnostic subgroups primarily divided on the basis of severity of mood elevation experienced during acute episodes. [2]

According to DSM 5, "For a diagnosis of bipolar disorder 1, it is necessary to meet the following criteria for a manic episode. The manic episode may be preceded by or followed by a hypomanic or major depressive episode.

Manic Episode

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).
B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behaviour
    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli as reported or as observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity). Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).
C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition. Note: A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.

Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder.

Hypomanic episode

A. Distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, lasting at least 4 consecutive days and present most of the day, nearly every day.

B. During the period of mood disturbance and increased energy and activity, three (or more) of the following symptoms (four if the mood is only irritable) have persisted, represent a noticeable change from usual behaviour, and have been present to a significant degree

    1. Inflated self-esteem or grandiosity.
    2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
    3. More talkative than usual or pressure to keep talking.
    4. Flight of ideas or subjective experience that thoughts are racing.
    5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
    6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation.

7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The episode is associated with an unequivocal change in functioning that is uncharacteristic of the individual when not symptomatic.

D. The disturbance in mood and the change in functioning are observable by others.

E. The episode is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization. If there are psychotic features, the episode is, by definition, manic.

F. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, medication, other treatment).

Note: A full hypomanic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a hypomanic episode diagnosis. However, caution is indicated so that one or two symptoms (particularly increased irritability, edginess, or agitation following antidepressant use) are not taken as sufficient for diagnosis of a hypomanic episode, nor necessarily indicative of a bipolar diathesis.

Note: Criteria A-'F constitute a hypomanic episode. Hypomanic episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder.

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure.

Note: To not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A-C constitute a major depressive episode. Major depressive episodes are common in bipolar I disorder but are not required for the diagnosis of bipolar I disorder." [5]

Similar to the DSM-5, World Health Organization's 11th revision of International Classification of Disease (ICD 11), divides bipolar disorders into bipolar I and bipolar 2 disorders, each having a similar set of diagnostic criteria. However, the ICD-11 still recognises mixed episodes. At least one past or present manic or mixed episode is necessary for the diagnosis of bipolar disorder 1. Although, depressive episodes are not always necessary. Contrarily, at least one hypomanic and one depressed episode must occur during the illness for bipolar disorder 2 to be diagnosed. [4]

Aetiology and Pathophysiology

There isn't a single theory explaining bipolar disorder's genetic, biochemical, pharmacological, anatomical, and sleep data. Transmitters (catecholamines, serotonin, gamma aminobutyric acid (GABA), glutamate, and others), hormones (brain-derived neurotrophic factor, thyroid, and others), and steroids are all the subject of biochemical research, both independently and together. Emerging imaging investigations in medicine could provide more information. [7]

Epidemiological research suggests that affective disorders are heritable, particularly studies of concordance in identical and fraternal twins. Depending on the diagnostic

criteria utilised, the morbid risk for family members of bipolar probands ranges from 2.9 to 14.5 percent for bipolar disorder and from 4.2 to 24.3 percent for unipolar illness.

The catecholamine hypothesis, which holds that mania is caused by an excess and depression is caused by a depletion of catecholamines, was developed as a result of biochemical and pharmacological experiments to explain bipolar disorder, particularly mania. Norepinephrine has been associated to depression mostly due to adverse effects, particularly the way tricyclic antidepressants (TCAs) can affect it. [7]

Because the dopamine precursor L-dopa, amphetamines, and TCAs frequently cause hypomania in bipolar patients, dopamine has been linked. Severe mania can be treated with antipsychotic drugs that specifically inhibit dopamine receptors, such as pimozide.

Numerous serotonin hypotheses have been put out, either alone or in connection with other systems. According to the "permissive hypothesis" of serotonergic activity, faulty dampening of other neurotransmitters, primarily norepinephrine, causes both manic and depressed states. [7]

Two other significant biochemical models for bipolar disorder exist. The increased frequency of episodes over time, as well as electrophysiological kindling and behavioural sensitization, are thought to be the causes of bipolar disorder, according to a model put forth by Post and collaborators. The following are examples of how this model and bipolar disorder are similar: Early episodes requiring precipitants whereas later episodes do not, recurrent episodes of one phase causing the appearance of the other, threshold effects (mild modifications eventually producing full-blown episodes), and predisposing effects of both genetic variables and early environmental stress. [7]

Desynchronization of the circadian rhythm has also been linked to bipolar disorder. According to animal studies, if two rhythms become de synchronized—that is, if one starts freely varying in and out of phase with the other—periodic physiological problems

may result. If and how genetics affect course (such as rapid cycling), circadian and seasonal rhythms, and the ability to kindle and sensitise are not clear. [7]

Even in euthymic bipolar patients, cognitive processing is frequently impeded.

There are deficiencies in executive function, visuospatial, memory, linguistic fluency, and attention. It is possible that this is a fundamental symptom of bipolar illness, secondary to other disorders such as insomnia, or secondary to co morbid conditions and coexisting conditions such as substance abuse. The assessment of adverse effects due to pharmacological treatment, the transition from inpatient to outpatient care, and the use of vocational rehabilitation to get ready for employment all underutilize cognitive assessment. [7]

The underlying causes of cognitive impairment in bipolar disorder patients are still not fully understood. Numerous research has shown that the causes of cognitive impairment in people with bipolar disorder are complex and include gene polymorphism, changes in brain structure and function, as well as inflammatory and metabolic factors. [9]

Major Cognitive Impairment in Patients with Bipolar Disorder and Its Possible Mechanisms

- **Attention impairment:**

A recent study done by Evelyn et al on "Performance of Bipolar Disorder Patients in Attention Testing: Comparison with Normal Controls and Among Manic, Depressive, and Euthymic Phases" found that in comparison to healthy controls, attention of patients with bipolar disorder was significantly affected, regardless of the stage of their disease, manic, depressive, or euthymic. [18]

The CHRNA7 gene has been linked to euthymic bipolar disorder patients' persistent attention deficit, while the CTCT haplotype has been linked to an increase in bipolar disorder patients' performance on attentional tasks. [19] A different study discovered that bipolar disorder patients with various ALDH2 genotypes experienced improvements in many cognitive function subcategories. On the other hand, some researchers think that the brain's metabolism may possibly play a role in the persistent attention impairment of euthymic bipolar disorder patients. [20]

In a study done by Brook et al,16 bipolar disorder patients in the stable phase and 11 healthy controls underwent continuous attention detection and head MRI scans, which showed that the patients' sustained attention was worse than that of the healthy controls and that the hippocampus, temporal lobe, and other brain regions were metabolised more slowly than usual. [21]

In conclusion, the studies mentioned above show how genetics and metabolism interact to cause attention impairment in bipolar disorder patients. [9]

- **Memory Impairment:**

Learning is the process by which people acquire their memories, which are continuous representations of their beliefs, experiences, and behaviours. Many researchers have looked at the causes underlying memory loss in bipolar disorder patients and think that, among other things, genetics and brain function may be involved. Speech memory impairment affects BIPOLAR DISORDER patients and their first-degree relatives, and this impairment may serve as a potential "endophenic" marker for the disease. [22] According to certain research, the dendritic development, neuron survival, synaptic plasticity, and memory acquisition were all correlated with the single nucleotide polymorphisms (SNPs) of bipolar disorder susceptibility genes. [23]

In a study done by Calabro Marco et al, relationship between bipolar disorder and several single SNPs in three strong candidate genes (CACNA1C, CHRNA7, and MAPK1) revealed that the distribution of the alleles for the genes crs1016388 in CACNA1; rs1514250, rs2337980, rs6494223, rs3826029, and rs4779565 in CHRNA7; in three different case groups suggesting that these 3 genes may play a role in bipolar disorder and subsequently affect the cognitive of bipolar disorder patients. [24]

- **Executive function impairment:**

Executive function, as defined by Alexander Luria (1966), consists of subjective intention, goal formulation, behavioural sequence planning in accordance with goals, target recognition for consistency with the cognitive route, route switching on time sequence, and evaluation of action outcomes. [9]

In a study done by, by Guiyun Xu et al, Executive function, episodic memory, visuospatial memory, verbal fluency, and information processing speed are all impaired in bipolar I, bipolar II, and unipolar depressive disorder patients during the acute depressive phase. [25]

Few studies have found that, in comparison to healthy people, bipolar disorder patients reported inferior executive functioning during stable periods or manic episodes. Additionally, it has been reported that the MsrA gene is linked to decreased executive function in people with bipolar I, and that the MsrA gene's rs4840463 polymorphism may enhance the chance of developing bipolar disorder 1 in the Chinese population. [26]

- **Other Aspects:**

The aetiology of bipolar disorder is influenced by neuroinflammation, and microglia activation is a key factor. Additionally, affective disorders have been linked to pathological changes in brain glial cells including oligodendrocytes and astrocytes, and one of the reasons lithium is useful in treating bipolar disorder may be connected to its anti-inflammatory action. [9]

Management of bipolar disorder:

Guidelines for management of bipolar disorder are given by various bodies namely,

- American Psychiatric Association 2002
- National Institute of Health and Care Excellence (NICE) 2014, updated 2020
- Canadian network for mood and anxiety treatment (CANMAT) and Internal Society for bipolar Disorder, 2018 and
- Clinical Practise Guidelines (CPGs), Indian Psychiatric Society (IPS) 2017[10]

Treatment of bipolar disorder can be difficult in a country like India since people there have few finances, little knowledge of the illness and its treatments, and insufficient access to medical facilities. Clinical Practise Guidelines (CPGs) for the management of bipolar disorder were originally developed by the Indian Psychiatric Society (IPS) in 2005. [11]

Making decisions regarding the therapy setting, the treatments to be used, and the areas to be treated will be part of the treatment plan formulation process. A treatment strategy must be developed in consultation with patients, carers, and other treatment team participants. The demands of the patient may inform treatment strategies, which can also

be realistic, doable, and adaptable. Additionally, the treatment strategy is periodically reviewed and changed in accordance with demands. [10]

Mood stabilisers, antidepressants, antipsychotic drugs, electroconvulsive therapy (ECT), supplementary medications, and psychosocial treatments can all be used as treatment options for bipolar disorder management. The stage of disease (mania/hypomania/depression/mixed) in which the patient presents to the doctor and prior treatment history are used to influence the use of various therapeutic approaches. Mood stabilisers are an integral part of bipolar disorder management. Lithium, valproate, lamotrigine, carbamazepine/oxcarbazepine, and topiramate are some of the mood stabilisers that are readily available. [11]

The first mood stabiliser used to treat bipolar disorder was lithium. It has been proven effective in managing acute episodes of either polarity as well as in preventing or relapsing into episodes of either polarity. It has been discovered that divalproex and its formulations (sodium valproate and valproic acid) are helpful in the management of bipolar disorder. It is effective in treating acute mania and mixed episodes, according to research. There is not as much support for its effectiveness in treating acute depression. Similar to lithium, when administered during the maintenance phase, it is also effective in preventing mania and depression. [11]

Lamotrigine's involvement in the treatment of bipolar disorder has been thoroughly investigated, and it has been found to be effective in the treatment of bipolar depression and in the prevention of depression recurrence. However, skin rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis, is the most feared adverse effects of lamotrigine. Oxcarbazepine, has shown of some benefit as monotherapy or add-on therapy in patients with refractory mania.[11]

Atypical antipsychotics like olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, amisulpiride, asenapine, ziprasidone, and haloperidol, among others, have been studied extensively in the last ten to fifteen years in both large multicentric double blind placebo controlled and active comparator randomised controlled studies. According to the results of these trials, antipsychotic medications such olanzapine, quetiapine, aripiprazole, risperidone, paliperidone, and ziprasidone are useful for treating acute mania. There is evidence to support the use of olanzapine and fluoxetine combined therapy, as well as quetiapine monotherapy, in the treatment of bipolar depression. Lurasidone has been shown to be effective in treating acute bipolar depressive episodes. [11]

There is evidence to show that the efficacy is higher and the onset of action is quicker when lithium or valproate is coupled with antipsychotics in the management of acute mania. Combinations may therefore be employed, depending on the intensity of the manic episode. [11]

The effectiveness of benzodiazepine additions to lithium, such as clonazepam and lorazepam, current level of evidence indicates that it is difficult to discern between these drugs' antimanic capabilities and the sedative effects of these substances. Consequently, these agents are thought of as additional agents, which may be effective in the treatment of acute episodes. [11]

The use of antidepressants in combination with mood stabilisers is preferable to the use of a mood stabiliser and a placebo and is not linked to an increased risk of manic switch, according to data from metanalysis. Paroxetine should be avoided if one wants to avoid using an antidepressant because it has been used in most of the research that did not find add-on antidepressants to be effective. Bupropion has been shown to have the lowest risk

of antidepressant-induced switch among the major antidepressants. However, it is crucial to keep in mind that antidepressants shouldn't be used as a stand-alone treatment. [11]

First-line medications for the treatment of manic episodes include lithium or valproate, olanzapine, haloperidol, quetiapine, aripiprazole, risperidone, paliperidone, or ziprasidone when used alone. [11]

In the Indian scenario, common antipsychotics including haloperidol, trifluoperazine, and chlorpromazine have also been employed. These are quite helpful in controlling irritability, anger, impulsivity, and psychotic characteristics. These, however, are linked to an increased risk of extrapyramidal responses. However, some research indicates that using lithium or valproate along with an antipsychotic may be more efficient than using any of these medications by themselves. Lithium is expected to have a slower beginning of action than the other drugs. Therefore, monotherapy should be tried if the mania is not too severe. However, combined therapy needs to be taken into consideration if mania is severe and accompanied by major disruption. It could be required to use adjunctive benzodiazepines for a brief period. Depot antipsychotics such risperidone, paliperidone, olanzapine, or a depot of a standard antipsychotic drug may be administered to patients who are uncontrollable and refuse medicine. [11]

The initial stage in management, if a patient presents with a "breakthrough" hypomanic/manic episode, entails optimising the current drug. Monitoring the serum levels of drugs like lithium and valproate can be used to optimise. Depending on how severe the episode is, further antipsychotics and benzodiazepines may be used. A second first-line agent must be added to the current course of treatment if the first-line agent taken at the recommended dose fails (fails to show significant clinical benefit after two weeks of use). Alternate approaches can involve switching from lithium to valproate or

vice versa, switching to carbamazepine, adding antipsychotic medicine if none had been taken previously, or switching the antipsychotic if it had. If the patient is extremely disruptive and not responding to a trial, ECT may be considered. The earliest possible time should be used to begin psychosocial interventions such family-focused interventions and patient and family psychoeducation. When the patient is cooperative, psychosocial therapies tailored to the patient, such as CBT or IPSRT, should be considered. [11]

While dealing with bipolar depression, the primary objective of management is to maintain euthymia, a normal level of functioning, and to refrain from manic or hypomanic episode. Of the many mood stabilizers, there is sufficient evidence to conclude that lithium and lamotrigine as the initial treatment options. In case of breakthrough episode, firstly to check for compliance and then optimise the dose. Lithium or lamotrigine may be taken into consideration if the patient is not currently on any mood stabilisers. Data suggests quetiapine monotherapy may also be advantageous among the antipsychotics. The use of fluoxetine and olanzapine together is also supported by data. Combining mood stabilisers or antipsychotics with antidepressants may be an option if the patient does not improve on monotherapy with these medications. Avoid taking antidepressants without also taking a mood stabiliser or an atypical antipsychotic. Benzodiazepines can be used when necessary. When the severity of the depression is mild to severe, psychosocial intervention in the form of CBT may also be taken into consideration. If depression is severe, there is a danger of harm to others, suicidality, or the patient is catatonic, pregnant, psychotic episode, ECT may be considered. [11]

It is generally accepted that the medication initiated during the acute phase of disease should be continued during the maintenance phase of treatment. Considering this, doctors may examine the patient's preference, clinical characteristics that may have an impact on the long-term result, episode recurrence, and side effects while choosing the medication during the acute episode. Lithium, valproate, or carbamazepine may be preferred if the patient experiences more manic episodes, while lithium, lamotrigine, or quetiapine may be considered if the patient experiences more depressed episodes. Combining lithium and valproate may be explored in extreme cases. [11]

Cognition in bipolar disorder:

Periods of exuberant and depressed mood are symptoms of bipolar disorder. There is data that suggests that cognitive impairment continues throughout euthymia. These mood episodes are linked to alterations in cognitive performance. It is unknown if the cognitive dysfunction develops as a result of the disease or as a result of the treatment. Bipolar disorder has been linked to specific verbal memory and executive function deficits. There is uncertainty over how pharmaceutical therapies affect cognitive performance, with numerous research presenting contradictory findings. The range of cognitive tests used, the study methodology, and the relatively small numbers of patients included all make it more difficult to interpret the data. Overall, there is some evidence to suggest that lithium both helps and hinders certain cognitive functions. Although this may depend on the patient demographic for whom they are prescribed, antipsychotics may have a negative impact on cognition. While the effects of other antiepileptic medications are uncertain, sodium valproate is likewise linked to lower cognitive results. The evidence is generally of poor quality and comes from a small number of studies that frequently fail to take into consideration the high variability of the condition and the related common comorbidities.

More precise conclusions may be drawn if studies were conducted in naturalistic environments and used consistent techniques and cognitive measurements. [27]

The term "cognition" refers to "thinking skills," such as the capacity for focus, memory, problem-solving, and planning. Cognitive development is unique to each person. Over the course of our lives, cognitive abilities might alter. With disease, injury, or getting older, they could get worse. Cognitive abilities can also be strengthened and enhanced at other periods. Drugs are crucial in the treatment of mood disorders like mania, sadness, and mixed episodes as well as in the prevention of brand-new episodes. Many people see an improvement in their cognitive function as a medication that begins to relieve their manic and depressive symptoms. Despite this, some drugs, especially when taken in high doses, can have negative effects on cognition. People frequently have difficulties paying attention, concentrating, recalling details, and solving problems when they are going through a depressed episode. Also impacted by manic episodes is cognition. The capacity to appraise a situation, pay attention, and control urges will be impaired. Thoughts will race and change in content. While some bipolar illness sufferers only encounter these difficulties during manic and depressive episodes, others continue to struggle with cognitive issues for months or even years after their mood symptoms have subsided. Reduced attention, learning and memory, planning, and decision-making may be a result of these issues. For many patients, bipolar disorder's essential characteristic—rather than just a side effect of medication or mood symptoms—is cognitive impairments. Therefore, since cognitive problems are symptoms of sickness, they should be evaluated and treated. Bipolar disorder patients who are older may face greater cognitive difficulties than those who are younger. However, bipolar disorder patients exhibit significant cognitive fluctuation. According to recent studies, 30–40% of bipolar illness sufferers typically score well on cognitive tests at a level appropriate for their age and educational level. A

similar percentage struggle with one skill, such as paying attention, while the remaining group struggle with numerous skills, including memory and thinking effectively. As a result, each person's cognitive functions are negatively impacted in a different way and to a different extent. [27]

Bipolar disorder 1 is characterised by neuropsychological dysfunction, and deficits are linked to poor functional outcomes. However, the results are constrained by a lack of knowledge regarding the relationship between psychotropic medication use and the level of observed impairment. A popular approach for treating acute mania is combination therapy, which involves a mood stabiliser plus an antipsychotic drug like risperidone or quetiapine. This treatment regimen is frequently continued after the mood episode has passed. Although post-hoc analyses have suggested an association between use of antipsychotics and decreased performance on tests of executive function involving inhibition, working memory, set-shifting, and verbal learning measures, the cognitive impact of mood stabilisers like lithium and valproate seems to be modest and limited to minor effects on memory. [28]

A longitudinal follow up study by Jan-Marie Kozicky et al on “Comparison of neuropsychological effects of Adjunctive risperidone or quetiapine in euthymic patients with Bipolar disorder 1” comparing the results of tests of executive function (working memory, set shifting, and inhibition), as well as verbal learning, between patients receiving maintenance treatment with mood stabiliser monotherapy (n = 15), adjunctive risperidone (n = 15), or quetiapine (n = 17), and a group of demographically matched healthy controls (n = 28). Despite having a comparable clinical profile, the study found that individuals using risperidone had significantly worse verbal learning, set-shifting, and working memory than those taking either mood stabiliser monotherapy or

supplementary quetiapine (P 0.05). Preliminary findings suggest that adding risperidone to a mood stabiliser has a negative impact on executive function and verbal learning, an effect not previously reported, even though randomised controlled trials are necessary to confirm the cognitive side effects of medications prescribed for maintenance treatment of bipolar disorder. There is not many research assessing the effects of different antipsychotic medications used in this population, despite links between antipsychotic usage and cognitive impairment in bipolar disorder 1 having been seen.[28]

According to a study by Carla Torrent et al., untreated euthymic patients performed better cognitively than those taking atypical antipsychotics. Although certain iatrogenic-pharmacologic effects cannot be completely ruled out, quetiapine appeared to be less linked to verbal memory impairment than olanzapine or risperidone. They advise using medications that have a lesser risk of negative cognitive effects as a result.[12]

A descriptive study was conducted by Ni Zu et al on "Pharmacological approaches in bipolar disorders and the impact on cognition" which found that lithium appears to have definite, yet subtle, negative effects on psychomotor speed and verbal memory, and that among the newer anticonvulsants, lamotrigine appears to have a better cognitive profile than carbamazepine, valproate, topiramate, and zonisamide, despite methodological flaws in the older studies and inadequate research regarding the newer agents. For a better understanding of the effects of atypical antipsychotics on neurocognitive functioning, both in monotherapy and in combination with other medications, more long-term research on bipolar disorder is required. Anti-depressants and cognitive enhancers are two more medications that have not yet received enough research in bipolar disorder. Bipolar disorder pharmacotherapies should be chosen to minimise neurocognitive adverse effects since these effects may already be hampered by the disease process.

Bipolar disorder patients may consider neurocognitive testing to more accurately assess the effects of treatment on neurocognition. [29]

Bipolar disorder patients are found to have both objective and subjective cognitive impairment, according to the evidence. One of the primary symptoms of bipolar disorder, which manifests in both the acute and remission stages, is objective cognitive impairment. This symptom is typically evaluated using a battery of neuropsychological tests. Subjective cognitive impairment, which is frequently reported by bipolar disorder patients, is defined as difficulties with attention, concentration, memory, perception, and emotion. [30] Despite patients' potentially compromised self-perception, a few studies have demonstrated that subjective cognitive function can be accurately assessed by self-reported standardised questionnaires. The term quality of life (QOL) describes how individuals with bipolar disorder view their level of physical, mental, and social wellness in various facets of life. Patients' decreased QOL continues to exist during the remission phase as well. [31]

The Bipolar Disorder Programme at the Hospital Clinic of Barcelona created COBRA, the first disease-specific scale to assess the subjective cognitive complaints encountered by bipolar disorder patients. The 16-item self-reported test assesses executive function, processing speed, working memory, verbal learning and recall, attention/concentration, and mental tracking." A 4-point Likert scale is used to rate each issue, with 0 denoting never, 1 sometimes 2 often, and 3 always." The subjective cognitive issues increase as the overall score increases from 0 to 48. [31]

MoCA is an instrument used to assess objective cognitive impairment. It is a brief and user-friendly instrument. It is a two-factor model, with the first factor, Memory, including subtests on delayed recall, language, sentence repetition, and orientation, and

the second factor, Attention/Executive Functions, including subtests on attention, executive function, and visuospatial abilities (cube copy and clock drawing). The MoCA scale has a total value from 0 to 30, with a higher score indicating greater objective cognitive performance. [31]

It is well-established that an individual's cognitive ability and their social and occupational function are consistently correlated. Recent research indicates that the cognitive performance of bipolar disorder sufferers, notably in the executive function and verbal memory domains, has a more negative impact on work outcomes than the disease's symptoms or sociodemographic characteristics. Clinical management needs to concentrate on the assessment of cognition and the impact of these changes on quality of life due to the high prevalence and extent of cognitive impairment in bipolar disorder, the early onset of these deficiencies, and their detrimental impact on the psychosocial and professional development of individuals. Additionally, as pharmacological treatments make up most of the how bipolar disorder is now managed. [29]

GAP IN EXISTING KNOWLEDGE

Major barriers in already existing regime and guidelines are the deficit in knowledge related to assessment and medication. We had planned to assess the impact of commonly used medications for bipolar disorder on cognitive function The study will give an insight regarding the prevailing practices and scope of improvement. To the best of our knowledge, very few study has been conducted to see the effect of pharmacological treatment over cognition in bipolar disorder 1 patients. Thus, we conducted this study to evaluate the effects of the same on cognition in bipolar disorder 1.

AIM AND OBJECTIVES

AIM

Evaluation of the effect of pharmacological treatment on cognition and safety of treatment regime in patients with bipolar disorder 1.

OBJECTIVES

PRIMARY

To evaluate the effect of pharmacological treatment on cognition in patients with bipolar disorder 1 at psychiatry outpatient department at AIIMS Bhopal.

SECONDARY

- To characterize the disease profile and drug utilization/prescription pattern of treatment regime prescribed in patients with bipolar disorder 1 at psychiatry outpatient department at AIIMS Bhopal.
- To evaluate the safety of treatment regime prescribed in patients with bipolar disorder 1.
- To validate Hindi version of Cognitive complaints in bipolar disorder rating assessment (COBRA).

MATERIALS AND METHODS

MATERIALS AND METHODS

1. STUDY DESIGN

This was a prospective observational cohort study. Patients satisfying inclusion and exclusion criteria were included. The study was conducted in accordance with ICH-GCP and after getting approval from Institutional Human Ethics committee, All India Institute of Medical Sciences, Bhopal, India (AIIMS letter number– IHEC-PGR/2021/PG/Jul/16 (Annexure), dated on 17th February 2022 and was conducted following the principles of the Declaration of Helsinki.

2. STUDY SITE

The study was done in Out Patient Department of Psychiatry in collaboration with Department of Pharmacology at All India Institute of Medical Sciences, Bhopal.

3. STUDY DURATION

Study was carried out from 1st March 2022 after getting approval from the IHEC-PGR, AIIMS Bhopal. Validity of questionnaire, data collection, data analysis and thesis compilation were done by October 2023.

4. STUDY POPULATION

Patients with bipolar disorder 1 of either gender visiting the outpatient department of Psychiatry as per the inclusion and exclusion criteria.

Inclusion Criteria:

- Age ≥18 years
- Confirmed diagnosis of bipolar disorder 1 requiring pharmacological treatment

- Euthymic patients with YMRS ≤10 and HAM-D ≤7
- Willing to give written informed consent

Exclusion Criteria:

- Patients with diagnosed psychiatric disorder other than bipolar disorder 1
- Presence of any neurological condition affecting cognition

5. SAMPLE SIZE:

An estimated sample size of 60 was reached, when power of the study was taken as 95% with 95% confidence interval, 5% alpha error, 0.5 effect size and 10% loss to follow up and calculated using G Power 3.1. However, after the end of the study we were able to achieve a sample size of 51 as initial 3-4 months were dedicated to the validation of Hindi translation of COBRA scale used for measuring cognition, hence effective data collection was of one year. Since, the patient inflow has decreased since COVID 19 and as our participant recruitment was inclusive of only those patients who were diagnosed with bipolar disorder 1 and were euthymic leading to recruitment of 51 patients.

6. STUDY PROCEDURE:

Patients who satisfied the inclusion criteria were invited to participate in the study. The patients were provided with participation information sheet and detailed explanation was given regarding the objective, risks and benefits of the study and their voluntariness of participation. There were assured that they can withdraw themselves any time during the study period and their treatment would not be hampered regardless of their decisions. The patients were recruited in the study after obtaining a written voluntary informed

consent from them. The routine clinical treatment protocol was not interrupted and no additional investigations was sought for the study purpose.

6.1 BASELINE DATA:

In this study data was collected by interviewing the patients and from their psychiatry OPD prescription at AIIMS Bhopal after the patient has given their informed consent.

Following data were collected at baseline in the case record form:

a) Patient's demographic details-

- Initials of the patient
- Unique hospital ID(UHID)/ Nikshay ID
- Age
- Gender
- Educational Qualification
- Address
- Contact number

b) Anthropometric measures of the patient-

- Weight
- Height

c) Pulse and Blood pressure

d) Smoking and alcohol status of the patient.

f) History of Bipolar disorder-

- Type

- Age at onset
- Episodes and its frequency
- Suicidal thoughts and attempts
- Past History of psychiatric illness and history of hospitalization
- Family history

g) Co-morbid conditions/ concurrent illness and drugs taken for them if any

h) Pharmacotherapy details-

- Date of prescription
- Drug name- generic or branded
- Drug dosage
- Dosage form
- Frequency of dose
- Route of administration
- Duration of treatment.

i) Evaluation of manic symptoms using YMRS scale.

j) Evaluation of depressive symptoms using HAM-D scale.

k) Evaluation of cognition using COBRA scale and MoCA scale.

6.2 FOLLOW-UP

After recruitment and baseline assessment, patients were followed up at 3-4 months and following data were collected:

a) Evaluation and scoring of cognition using COBRA scale and MoCA scale.

b) Evaluation of manic symptoms and scoring them using YMRS scale.

c) Evaluation of depressive symptoms and scoring them using HAM-D scale.

d) Details of drugs added/dose adjusted/withdrawal.

e) Details of adverse events including type, severity, frequency, onset, and progression/resolution followed by causality assessment.

f) Details of adherence to medications using Medication Adherence Rating Scale (MARS).

7. OUTCOME PARAMETERS

Primary Outcome Parameters:

Effectiveness of pharmacological treatment on cognition in patients with bipolar disorder 1 using COBRA score and MoCA scale

Secondary Outcome Parameters:

1. Prescription pattern of drug/drug regimens

2. Assessing the severity of ADR using Hartwig severity assessment scale

3. Causality assessment of the ADRs using WHO-UMC scale

4. Assessing medication adherence of patients using MARS scale

8. DATA ANALYSIS

8.1 Evaluation of the effect of pharmacological treatment on cognition in patients with bipolar disorder 1:

- Cognition was assessed with COBRA scale and MoCA scale in patients with bipolar disorder 1 who met the inclusion and exclusion criteria and were euthymic according to YMRS and HAMD scales.

- In order to evaluate mania and depression, we used YMRS and HAM-D scales respectively at baseline and at follow up. YMRS score of ≤10 and HAM-D score of ≤7 was considered euthymic.

a. Young Mania Rating Scale:

The scale has 11 items based on the patient's subjective report of his/her clinical condition. There are four items that are graded on 0-8 scale (irritability, speech, thought content, and disruptive/aggressive behaviour) while the remaining seven items are graded on 0-4 scale. These four items are given twice the weight of the others to compensate for poor cooperation from severely ill patients. [32]

Total score:	**Interpretation**
≤ 12	Remission
13-19	Minimal symptom
20-25	Mild mania
26-37	Moderate mania
38-60	Severe mania

b. Hamilton Depression Rating Scale:

The HDRS (also known as the Ham-D) is one of the most widely accepted clinician-administered depression assessment scale. For the HDRS, a score of 0-7 is generally considered to be within the normal range (or in clinical remission. [33]

Total score:	**Interpretation**
0-7	None

8-16	Mild
17-23	Moderate
≥24	Severe

- Once the patients met the inclusion criteria, cognition was assessed with COBRA and MoCA scales.

a. Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA)

- COBRA is a self-reported instrument that was established by the Bipolar Disorder Program in Barcelona to measure subjective cognitive impairments in patients with bipolar disorder. The COBRA utilizes queries informed by everyday mental tasks.
- Sixteen items, including verbal learning and memory, executive functionality, attention/concentration, working memory, processing speed, and mental tracking, are used to measure subjective cognitive dysfunction. A four-point scale is used to rate these items (0 = never, 1 = sometimes, 2 = often, and 3 = always)
- The total COBRA score is calculated by adding the rating of each item; the highest possible score is 48, and scores of ≥15 indicate moderate to severe subjective cognitive impairment. [34]

b. Montreal Cognitive Assessment (MoCA)

- MoCA is a widespread and concise tool for the assessment of cognitive impairment. MoCA is a one-page 30-point test administered in 10 minutes.
- Details on the specific MoCA items are:
    - The short-term memory recall task (5 points) involves two learning trials of five nouns and delayed recall after approximately 5 minutes.

- Visuospatial abilities are assessed using a clock-drawing task (3 points) and a three-dimensional cube copy (1 point).
- Multiple aspects of executive functions are assessed using an alternation task adapted from the Trail Making B task (1 point), a phonemic fluency task (1 point), and a two-item verbal abstraction task (2 points).
- Attention, concentration, and working memory are evaluated using a sustained attention task (target detection using tapping; 1 point), a serial subtraction task (3 points), and digits forward and backward (1 point each).
- Language is assessed using a three-item confrontation naming task with low-familiarity animals (lion, camel, rhinoceros; 3 points), repetition of two syntactically complex sentences (2 points), and the fluency task.
- Finally, orientation to time and place is evaluated (6 points). Clinical cut off score recommended is 26. [35]

Total Score	**Interpretation**
≥ 26	Normal
18-25	Mild cognitive impairment
10-17	Moderate cognitive impairment
<10	Severe cognitive impairment

8.2 Evaluation of the safety of treatment regime prescribed in patients with bipolar disorder 1:

The safety profile of each drug being prescribed in different regimens by direct questioning and spontaneous reporting of adverse events. Any occurrence of adverse event during the entire course of treatment was documented and reported to the Adverse

Drug Reaction Monitoring Centre at AIIMS, Bhopal. Adverse Events assessment including nature, type, severity and frequency followed by Causality assessment. Severity was assessed using Hartwig severity scale and the causality assessment was carried out based on WHO-UMC Scale.

a. Hartwig Severity Scale

Adverse drug reactions are considered among the leading causes of morbidity and mortality. This scale is used for severity assessment. Depending upon the severity of the suspected reaction, this scale is divided into three categories. They are mild, moderate, and severe. They also have 7 levels.

In the mild type reaction level 1 requires no change in treatment with the suspected drug whereas in level 2 the ADR requires that the suspected drug to be withheld, discontinued or otherwise changed. No antidote or other treatment is required, and there is no change in the length of stay. For moderate reactions, level 3, the suspected drug should be stopped, discontinued, or otherwise changed, and an antidote or other treatment is required. There is no increase in the length of hospital stay for these patients. But level 4(a) is level 3 reactions that increase the length of stay by at least one day, whereas level 4(b) the ADR is the reason for the hospital admission. In the severe type of ADR, level 5 are reactions which require intensive care unit attention. Level 6 reactions cause permanent harm to the patient, whereas in level 7, ADR leads to the death of the patient either directly or indirectly.[35]

b. WHO-UMC Assessment scale

The WHO-UMC system has been developed in consultation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a

practical tool for the assessment of case reports. It is basically a combined assessment considering the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. Since pharmacovigilance is particularly concerned with the detection of unknown and unexpected adverse reactions, other criteria such as previous knowledge and statistical chance play a less prominent role in the system. It is recognised that the semantics of the definitions are critical and that individual judgements may therefore differ. There are other algorithms that are either very complex or too specific for general use. This method gives guidance to the general arguments which should be used to select one category over another. It uses four main criteria – time relationship between drug use and the adverse event, presence/ absence of other competing causes, response to drug dechallenge and response to rechallenge to assess the causality. Here there was six classes of probability- certain, probable, possible, unlikely, conditional and unclassifiable. [36]

8.3 Evaluation of the adherence to medications using Medication adherence rating scale (MARS) in patients with bipolar disorder 1

MARS, is a 10-item yes/no self-report instrument. It was developed from two existing scales, the 30-item Drug Attitudes Inventory, and the 4-item Medication Adherence Questionnaire with the aim of developing a more reliable and valid tool for assessing medication adherence behaviour in psychosis.

- Total scores range from 0 (low likelihood of medication adherence) to 10 (high likelihood).
- A cut-off score of 6 on the MARS was considered to divide the sample into two groups. [37]

Total score	Interpretation
≥6	Good adherence
< 6	Poor adherence

8.4 Evaluation of the disease profile and drug utilization/prescription pattern of treatment regime in patients with bipolar disorder 1:

The prescription pattern was assessed based on patient's demography, drug name, dosage form, strength, dose, frequency of administration, duration of treatment, diagnosis of the patient.

9. VALIDATION OF HINDI VERSION OF COGNITIVE COMPLAINTS IN BIPOLAR DISORDER RATING ASSESSMENT(COBRA) SCALE

COBRA is a self-reported instrument that was established by the Bipolar Disorder Program in Barcelona to measure subjective cognitive impairments in patients with bipolar disorder. The COBRA utilizes queries informed by everyday mental tasks.

- Sixteen items, including verbal learning and memory, executive functionality, attention/concentration, working memory, processing speed, and mental tracking, are used to measure subjective cognitive dysfunction.
- A four-point scale is used to rate these items (0 = never, 1 = sometimes, 2 = often, and 3 = always)
- The total COBRA score is calculated by adding the rating of each item; the highest possible score is 48, and scores of ≥15 indicate moderate to severe subjective cognitive impairment. [38]

Rosa et al translated the original Spanish version into the English version. It would be of great significance to translate the COBRA into Hindi version to assess cognitive deficits reported by patients of bipolar disorder who are not well versed in English language. The main aim of this validation study is to examine the psychometric properties of the COBRA among Hindi speaking bipolar patients. [34]

9.1 Subjects:

All Hindi speaking patients meeting the inclusion criteria were enrolled in the study. The healthy comparison group (controls) was recruited from the general population within the premises of AIIMS Bhopal campus. We also ensured that controls had no first-degree relatives with bipolar disorder or other psychiatric disorders. Informed consent was obtained from each subject after a complete verbal description of the validation study.

9.2 Assessments:

The English version of COBRA was used to translate into its Hindi version in which the process of translation was divided into the following 4 stages:

- Forward translation
- Backward translation
- Linguistic adaptation
- Pilot study

Firstly, the initial translation from the English language to the Hindi language was made by two independent translators. As bilingual translators should translate the questionnaire into their mother tongue, hence, one translator, aware of the concepts regarding the questionnaire provided a translation that more closely resembles the original instrument,

and the other translator, who was unaware of the objective of the questionnaire, produced the second translation. One of the junior residents from the department of Pharmacology, AIIMS, Bhopal and the Hindi cell at AIIMS Bhopal translated English version into Hindi, respectively. The two translations were submitted to the experts for examining and comparing in order to reach a single translation by consensus.

To ensure the accuracy of the translation, a back translation was done by two independent translators who were unaware of the intended concepts which the questionnaire measures. Both the forward and backward translation was done to ensure its conceptual equivalence.

Finally, all the translators participated in the proof-reading test and the final Hindi version was established. After which, the Hindi version was then reviewed by a panel of experts (psychiatrist, psychologist, investigators, and translators).

Next, we used the Hindi version of the COBRA for a pilot study to evaluate the readability, simplicity, acceptability, etc., amongst euthymic bipolar disorder patients in the psychiatric OPD of AIIMS, Bhopal hospital. According to the feedback appropriate modifications were done to finalize Hindi version of the COBRA for validation.

9.3 Validity and reliability assessment:

- COBRA was administered twice to the same subjects 2 weeks apart and their scores were used for calculating Intra-class correlation coefficient between the COBRA scores of these two assessments. The internal consistency of the COBRA was examined by Cronbach's alpha and the test- retest reliability.
- Concurrent validity for the COBRA was assessed by investigating the association between the COBRA and MoCA (Montreal Cognitive Assessment)

- Discriminative validity to detect the differences between bipolar disorder 1 patients and healthy controls was analysed by the statistical test.
- The optimal point for the COBRA was determined by means of Receiver operating characteristic (ROC) curve to measure the scale's discriminative capacity between patients and controls by means of ROC curve.
- Feasibility was described as the percentage of patients and controls who did not respond to each item in the questionnaire. [38]

10. STATISTICAL ANALYSIS:

All the data collected during the study were be recorded on the case record form and then was tabulated in Microsoft excel. The data was analysed using statistical software package SPSS version 26.0. All the acquired data were checked for normality by plotting histograms and applying Shapiro-Wilk hypothesis test. As the sample data was found to be significantly different from the normal population, non-parametric tests were applied. Categorical variables such as gender, educational status, history of hospitalization, suicidal thoughts and attempts, smoking status, intake of alcohol, presence of any co-morbidities, category of cognition seen on COBRA, MoCA scales, classes of drugs used were calculated using frequencies and proportions. Continuous variables like age, age at onset, weight, height, duration of illness, YMRS score, HAMD score, COBRA score, MoCA score, number of drugs, MARS score, follow up scores of YMRS, HAMD, COBRA and MoCA scales and number of drugs were calculated using median with inter quartile range. Change in cognition score between baseline and follow up was analysed using Wilcoxon signed rank test. Mc Nemur test was used to analyse the change in category of cognition from baseline to follow up when assessed with COBRA scale, and

Fischer's exact test was used to analyse change in categories from baseline to follow up when assessed with MoCA scale. Spearman correlation test was used to compare the influence of other factors such as age, age at onset, gender, weight, height, duration of illness, educational status, history of hospitalization, suicidal thoughts and attempts, smoking status, intake of alcohol, presence of any co-morbidities and medication adherence on cognition. A p-value of less than 0.05 was considered statistically significant.

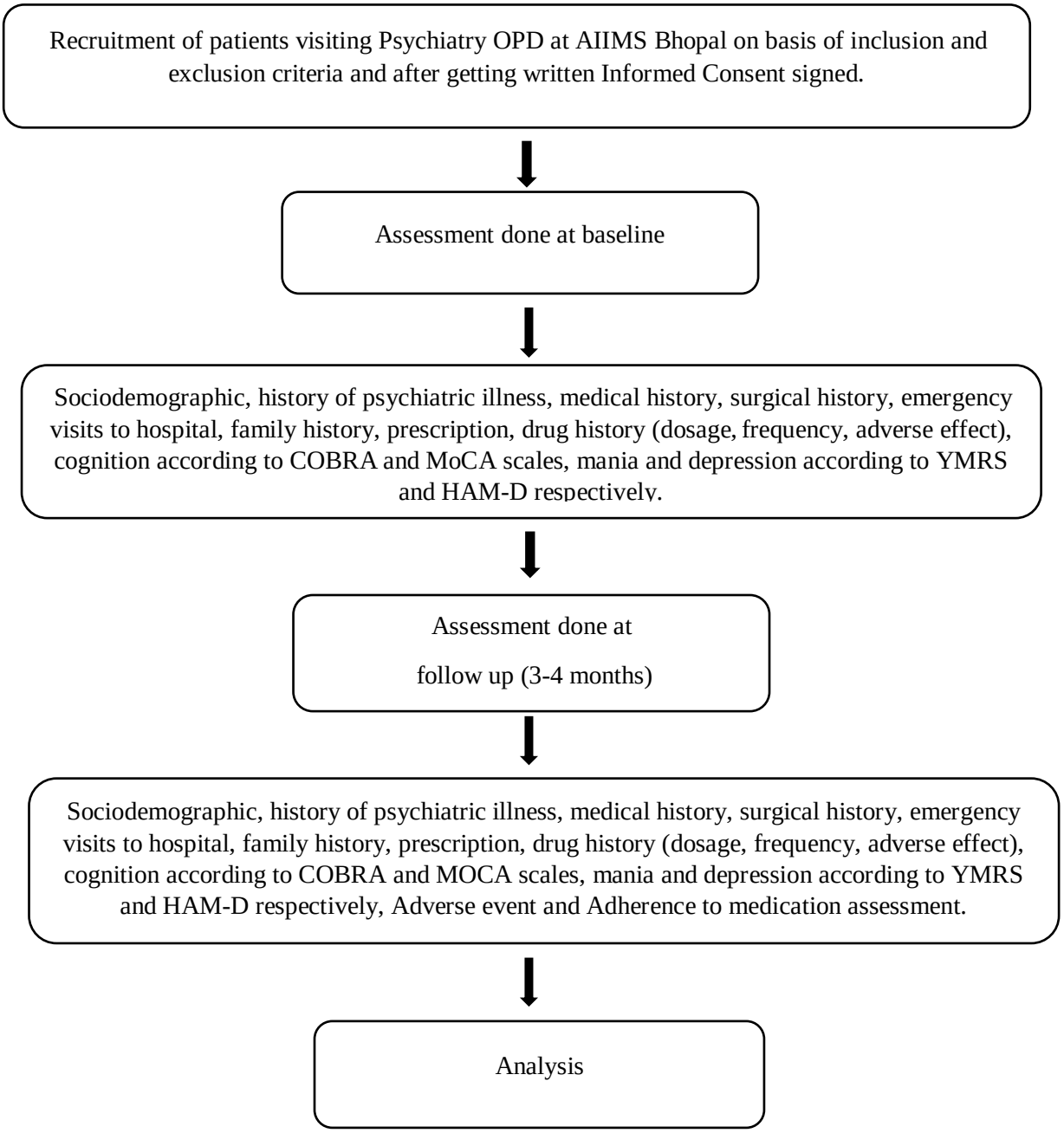
11. ETHICAL CONSIDERATIONS

The study was done following the principles of the Declaration of Helsinki and in accordance with the International Conference on Harmonization (ICH)- Good Clinical Practice (GCP) and ICMR Ethical Guidelines for Biomedical Research in Human participants. The patients were informed by the investigator both orally and in writing about the scopes, purpose, possible benefits, and associated risk (if any) of the study in a very simple and local language understandable to the patient. The investigator was solely be responsible to ensure that the patient understands about the entire study, including whom to contact in case of any questions arising during the study. They were informed that the medical records and other data obtained were analysed without any loss of confidentiality. The patient was then asked to sign the "Informed Consent Form" to signify that they have understood the details as explained to them and have agreed to be included in this study. The signature of the investigator was also obtained on the "Informed Consent Form".

12. CONFIDENTIALITY OF DATA

Data collected from the patients were entered in data collection sheets (case record forms) and safely secured in locked steel cupboards kept in the Department of Pharmacology, AIIMS Bhopal, under the custody of the investigators. Electronic patient data were saved in password protected files and folders in computers and laptops under the custody of the investigators in the department of Pharmacology, AIIMS, Bhopal. Only investigators involved in this study were able to access these data. All such information collected during the study was used for the purpose of research only. The results of the study may be published as group data and patient's individual identity will not be revealed at any point.

STUDY FLOWCHART


Recruitment of patients visiting Psychiatry OPD at AIIMS Bhopal on basis of inclusion and exclusion criteria and after getting written Informed Consent signed.
Assessment done at baseline
Sociodemographic, history of psychiatric illness, medical history, surgical history, emergency visits to hospital, family history, prescription, drug history (dosage, frequency, adverse effect), cognition according to COBRA and MoCA scales, mania and depression according to YMRS and HAM-D respectively.
Assessment done at
follow up (3-4 months)
Sociodemographic, history of psychiatric illness, medical history, surgical history, emergency visits to hospital, family history, prescription, drug history (dosage, frequency, adverse effect), cognition according to COBRA and MOCA scales, mania and depression according to YMRS and HAM-D respectively, Adverse event and Adherence to medication assessment.
Analysis

RESULTS

RESULTS

A total of 51 participants were recruited during the study period of February 2022 to September 2023, during which initial 3 months were dedicated to validation of the Hindi version of the study rating scale (COBRA). One participant was lost to follow up, allowing the analysis of data of 50 participants for the assessment of study objectives requiring follow up.

1. General baseline characteristics of study patients

1.1 Demographic details

Data from a total of 51 bipolar disorder 1 patients was collected at baseline, out of which 31 (60.8%) were male and 20 (39.2%) were female in the ratio of 1.5:1 **(Figure1)**. In parameters where the variability was found to be high, median was used to denote the average values. The median age of the participants was 39 years (IQR: 23-49 years) while the mean age was 36.88 (SD: ±13.26) years **(Figure 2)**. Out of the 51 participants, 15 (29.4%) fell in the age group of 18- 25 years and 36 (70.6%) were of age greater than 25 years. Median age of onset of bipolar disorder 1 was 27 years (IQR: 20-38 years) and median duration of illness was 05 years (IQR: 2-10 years). In terms of educational status, 28 (54.9%) patients were graduate/post graduate, 06 (11.7%) had completed their intermediate degree, while 14 (27.5 %) had different levels of school certificate **(Figure 3)**.

Table 1 shows demographic characteristics of the participants.

Table 1: Demographic characteristics of the participants

S. No	Characteristics	Value (N = 51) n (%) / Median (IQR) / Mean ± SD
1.	Median age	39 years (IQR: 23-49 years)
2.	Mean age	36.88 years (SD: ±13.26 years)
3.	Age 18-25 years	15 (29.4%)
4.	Age > 25 years	36 (70.6%)
5.	Median age of onset	27 years (IQR: 20-38 years)
6.	Median duration of illness	05 years (IQR: 02-10 years)

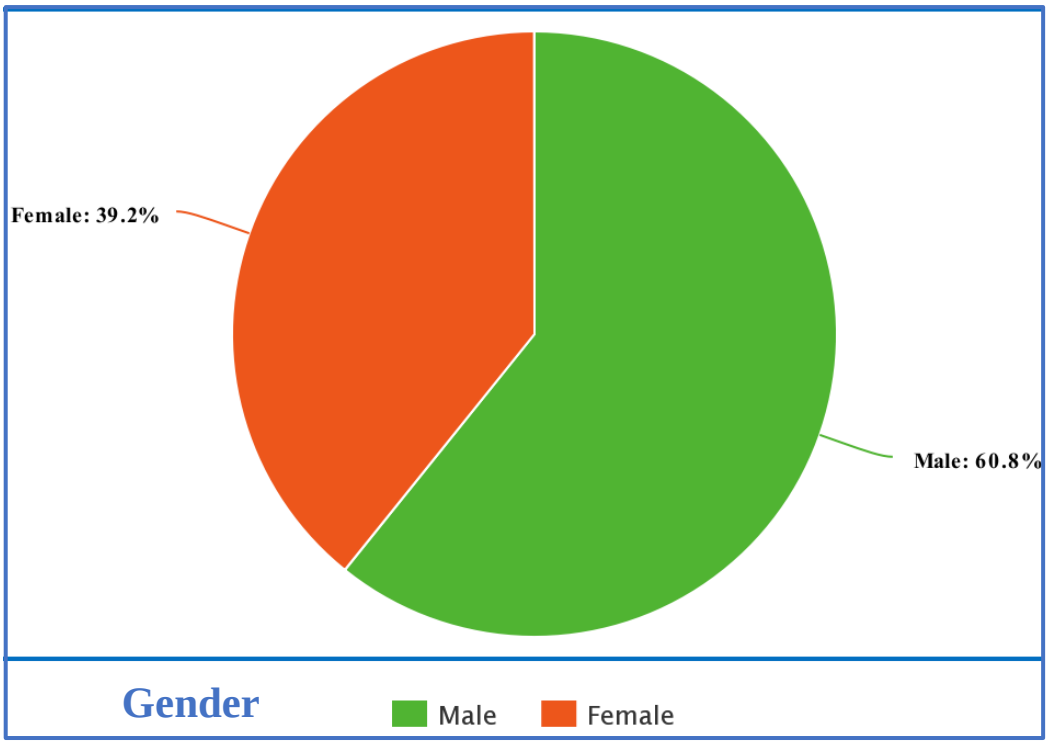


Figure 1: Gender distribution

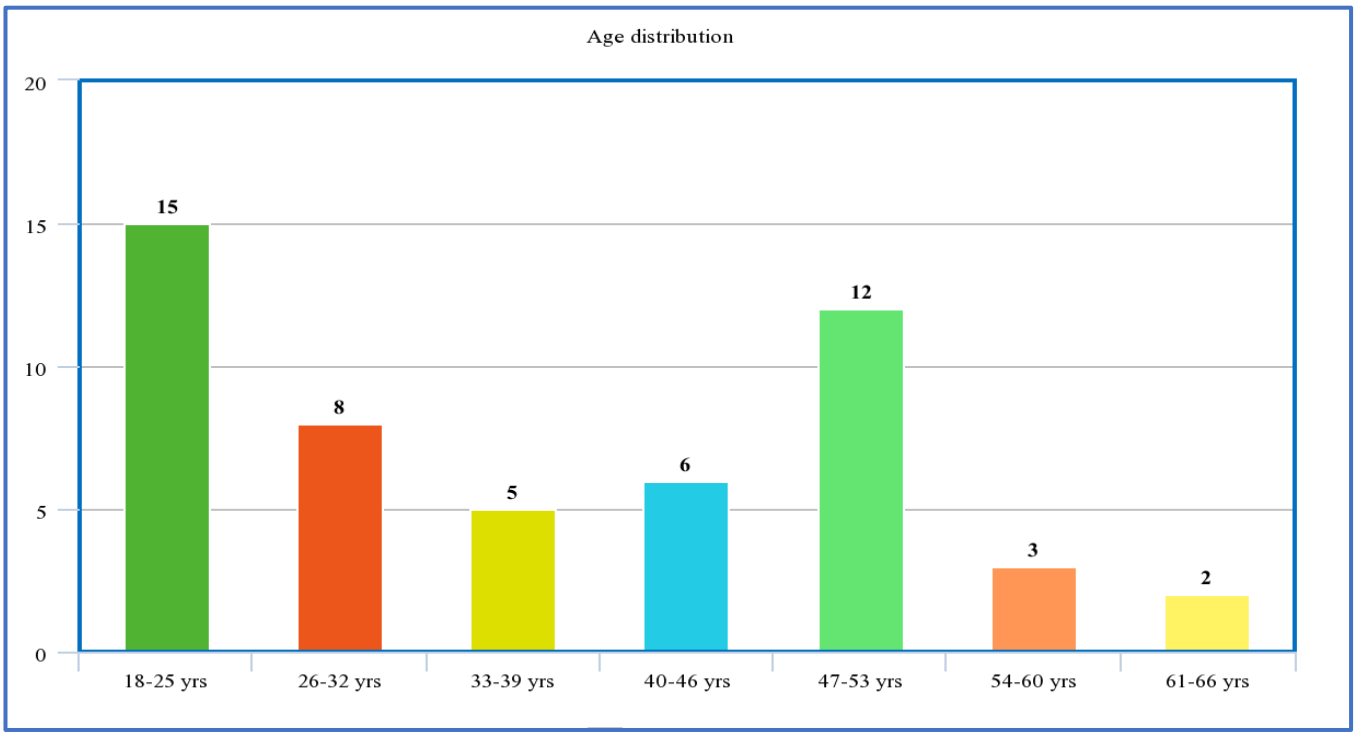


Figure 2: Distribution of age

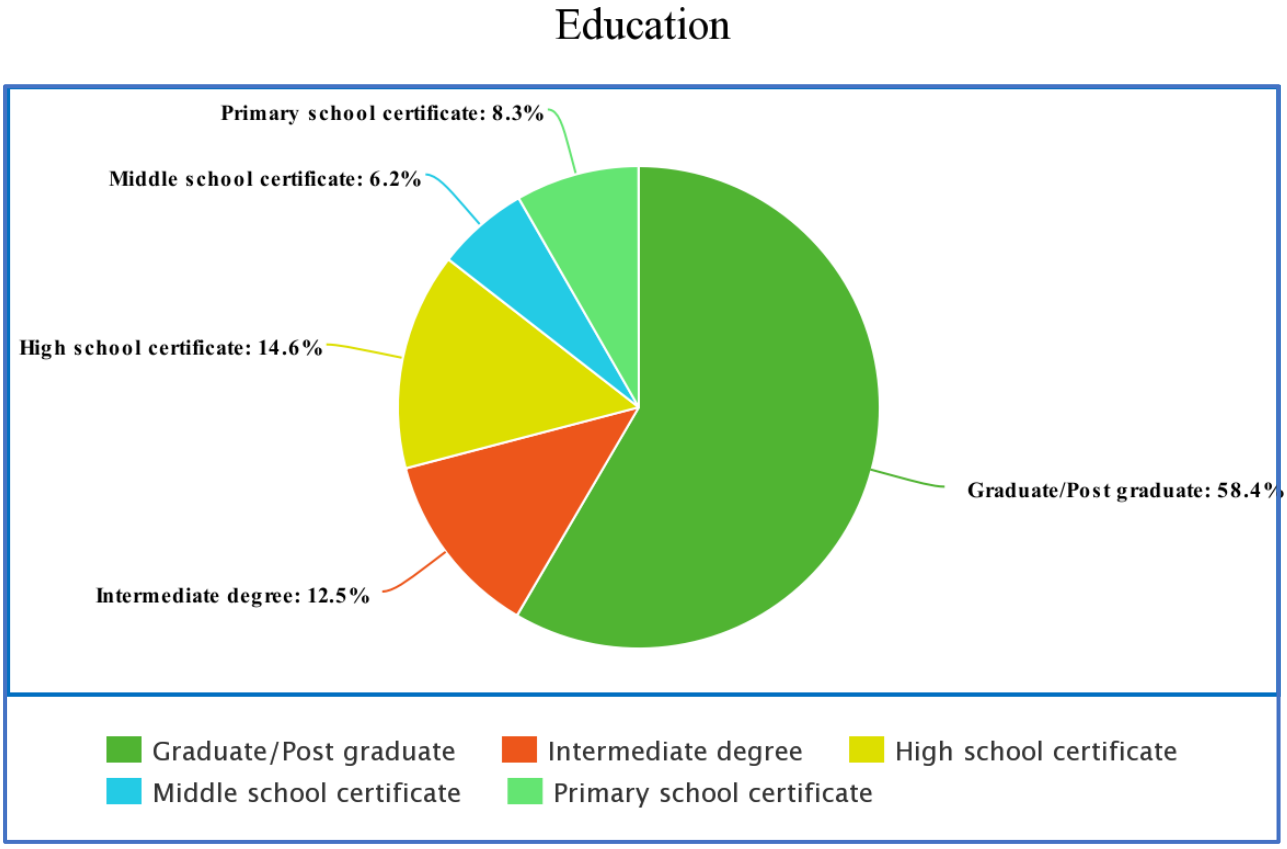


Figure 3: Educational status

1.2 Physical characteristics

The participants had a mean body weight of 69.51 kg (SD: ±13.11), **(Figure 4)**, and median height of 162.5cm (IQR: 157.9-175.2 cm) while the mean height of 165.84 cm (SD: ±9.15), **(Figure 5)**. Table 2 shows the physical characteristics of the participants

Table 2: Physical characteristics of the participants

S. No	Characteristics	Value (N = 51) Median (IQR) / Mean ± SD
1.	Mean body weight (kg)	69.51 (SD: ±13.11)
2.	Mean height (cm)	165.84 (SD: ±9.15)
3.	Median height (cm)	162.5 (IQR: 157.9-175.2)

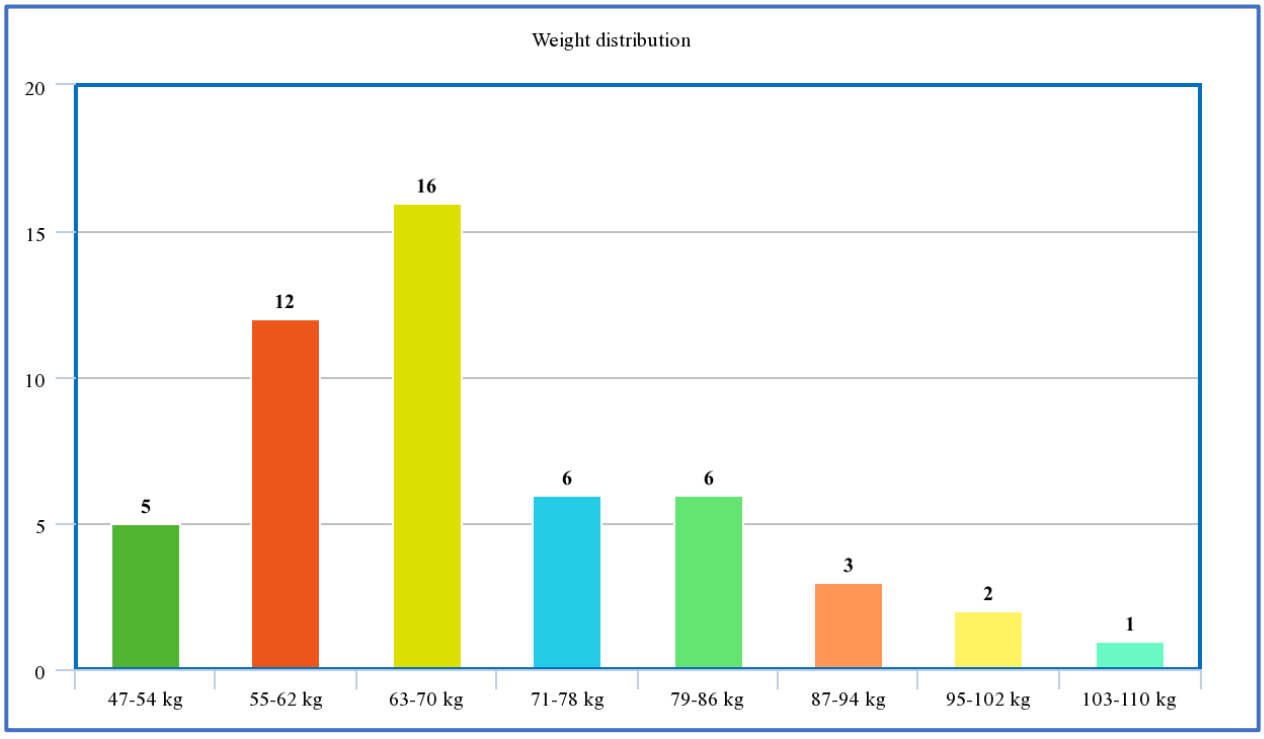


Figure 4: Distribution of body weight

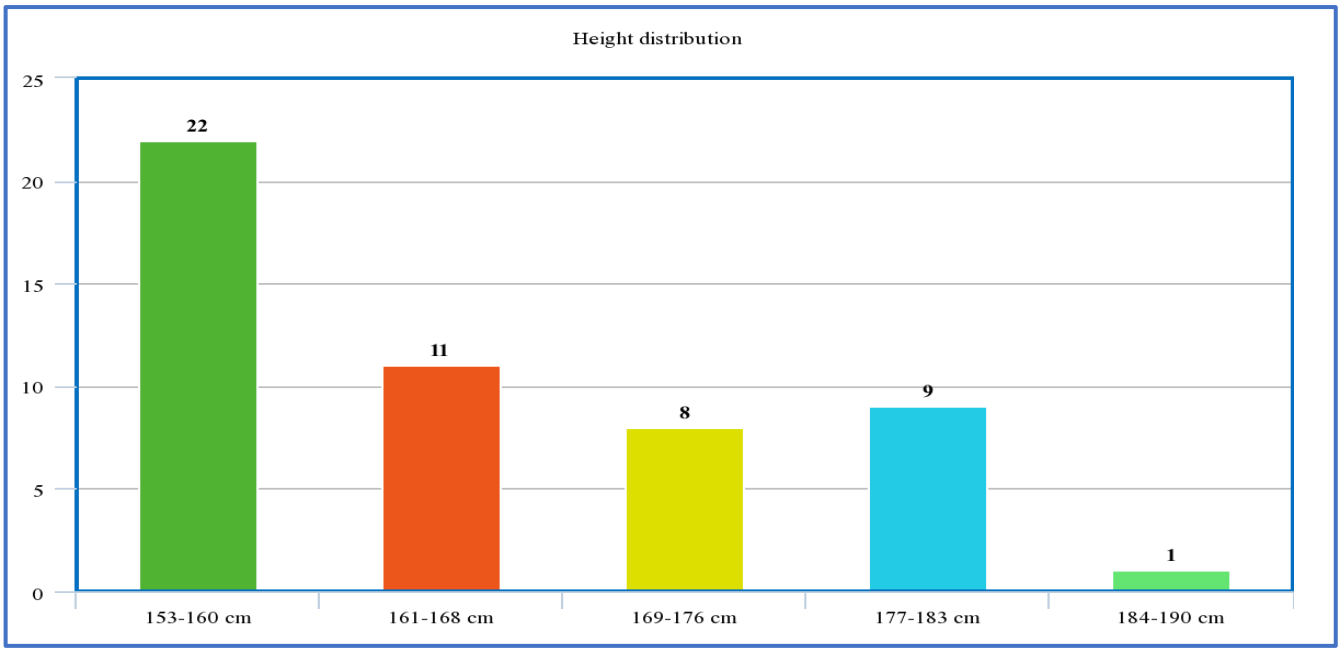


Figure 5: Distribution of height

1.3 Smoking and alcohol use

Among the 51 participants, 49 (96.1%) participants did not smoke and the rest 02 smoked approximately one cigarette daily **(Figure 6).** Also, 05 (9.8%) out of 51 participants used to have alcohol occasionally **(Figure 7)**.

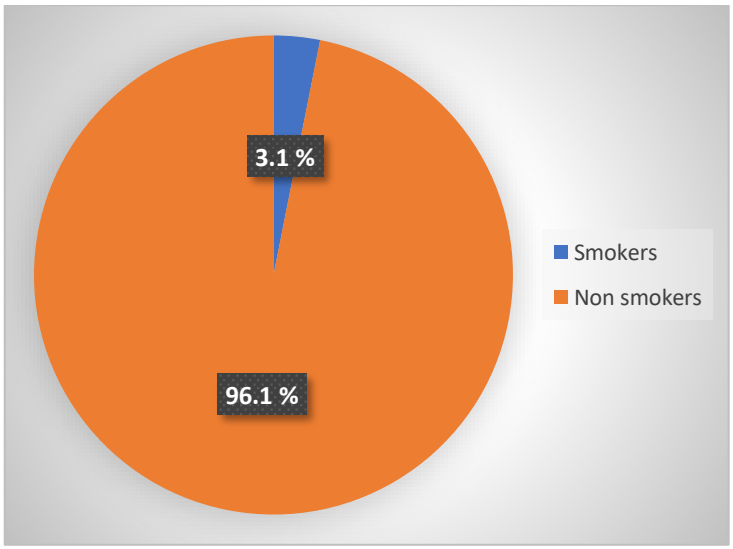


Figure 6: Proportion of smokers and non-smokers

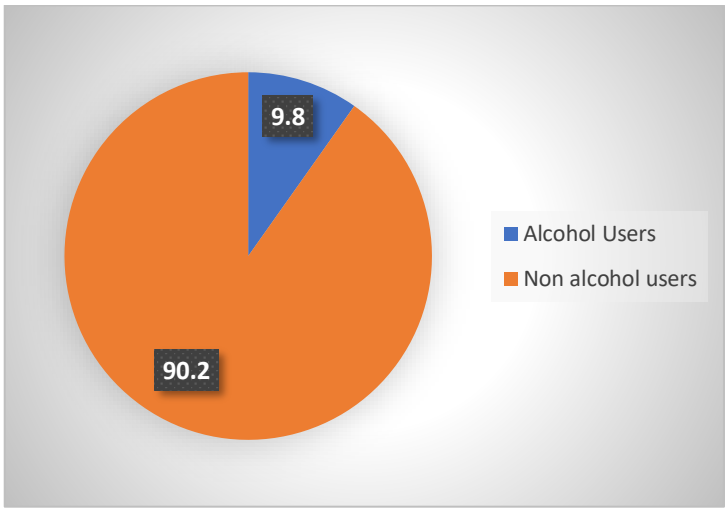


Figure 7: Proportion of alcohol users and non-alcohol users

1.4 Suicidal thoughts and suicidal attempts

Among the 51 participants, 11 (21.6%) patients had suicidal thoughts and 07 (13.7%) participants had attempted suicide once in the past, for which they had a history of hospitalization.

1.5 Family history

Among the 51 participants, 05 (9.8%) had family history of bipolar disorder, although the type of bipolar disorder was unknown.

1.6 Associated co-morbid conditions

Out of the 51 participants, 06 (11.8%) participants had associated co-morbidities such as type 2 diabetes mellitus (T2DM), hypertension, and hypothyroidism. All the participants were on concurrent treatment for their co-morbidities.

Table 3 shows different co-morbidities seen in the participants.

Table 3: Co morbidities in participants

S. No	Co morbidities	Value: n (%)
1	Type 2 diabetes mellitus	03 (50%)
2	Hypothyroidism	02 (33.3%)
3	Hypertension	01 (16.6%)

2. Baseline clinical characteristics of participants:

2.1 Baseline clinical scores:

Median score for participants considered euthymic as per YMRS and HAMD scales were 0 (IQR: 0-1) each. On applying cognitive scales, median COBRA score was 06 (IQR: 1-12) and MoCA score was 25 (IQR: 20-28). On categorising participants as per COBRA score, 40 (78.4%) patients were normal on the cognition scale and 11 (21.5%) had moderate to severe cognitive impairment. As per MoCA score, 22 (43.13%) patients were normal on the cognition scale, 24 (47.1%) had mild cognitive impairment and 05 (9.8%) had moderate cognitive impairment. Table 4 shows baseline clinical characteristics of the participants.

Table 4: Baseline clinical characteristics of the participants

S No	Characteristics	Value (N = 51) Median (IQR)
1.	Mania: Median YMRS score	0 (IQR: 0-1)
2.	Depression: Median HAM D score	0 (IQR: 0-1)
3.	Cognition: Median COBRA score	06 (IQR: 1-12)
4.	Cognition: Median MoCA score	25 (IQR: 20-28)

2.2 Medications:

The median number of drugs participants were on was 02 (IQR: 2-3). Participants were prescribed with different classes of drugs, namely, 16 (31.3%) participants on mood stabilizers, 10 (19.6%) on anti-psychotics, 22 (43.1%) on a combination of a mood stabilizer and an anti-psychotic and 03 (5.88%) participants were on a combination of a mood stabilizer, an anti-psychotic and an anti-depressant

(Figure 8). Other concomitant medications prescribed to the participants were zolpidem, metformin, telmisartan, atorvastatin, L- thyroxine and folic acid.

Table 4 mentions medication details with different classes of drugs prescribed along with the individual drugs prescribed under each category.

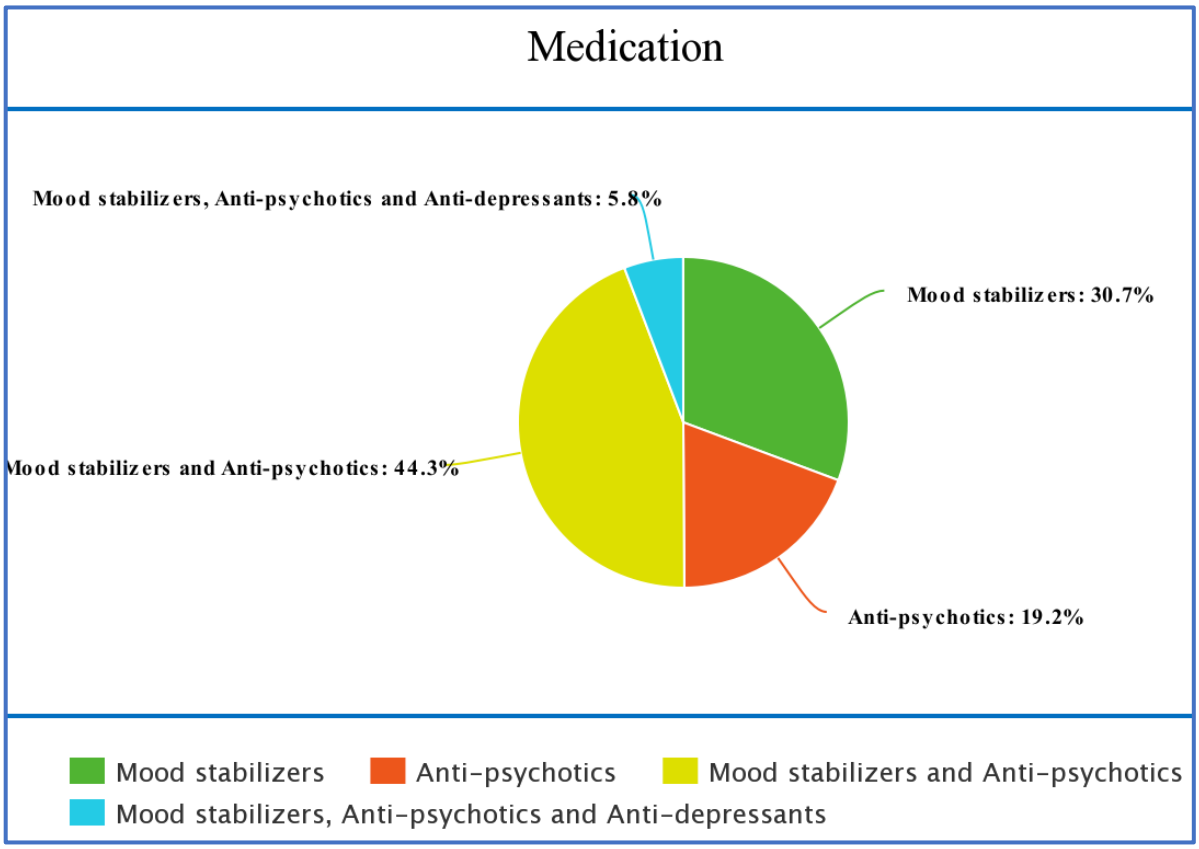


Figure 8: Classes of drugs prescribed

Table 5: Medications prescribed to the participants for bipolar disorder 1

S No.	Medications	Value (N = 51) n (%)
1.	**Mood stabilizers**:	**16 (31.3%)**
1a	Lithium:	02
1b	Divalproex sodium	11
1c	Lithium and Divalproex sodium:	03
2.	**Anti-psychotics:**	**10(19.6%)**
2a	Olanzapine:	04
2b	Quetiapine:	04
2c	Aripiprazole:	02
3.	**Mood Stabilizers and anti-psychotic:**	**22(43.1%)**
3a	Lithium and olanzapine:	07
3b	Lithium and aripiprazole:	03
3c	Divalproex sodium and olanzapine:	08
3d	Divalproex sodium and quetiapine:	03
3e	Divalproex sodium and aripiprazole:	01
4.	**Mood stabilizer, anti-psychotic and anti-depressant:**	**03(5.88%)**
4a	Divalproex sodium, olanzapine and fluoxetine:	01
4b	Divalproex sodium, quetiapine and fluoxetine:	01
4c	Lithium, olanzapine and fluoxetine:	01

3. Follow up data of study participants:

Follow up of study participants was done between 3-4 months after baseline assessment. The mean duration of follow up of the participants was 111 days (±24.02 days)

3.1 Assessment of mania and depression:

Median score for participants as per YMRS and HAMD scales for mania and depression, respectively, remained zero. (Shapiro Wilk test for normality indicated a non-normal distribution of scale scores)

3.2 Assessment of cognition:

On applying cognitive scales, the median COBRA score at follow up was 1.5 (IQR: 0-6) and MoCA score was 27 (IQR: 26-28.25). Upon categorising participants as per COBRA scoring, 47 (92.2%) participants were normal on the cognition scale and 03 (5.9%) had moderate to severe cognitive impairment. As per MoCA scoring criteria, 38 (74.5%) participants were normal on the cognition scale and 12 (23.5%) had mild cognitive impairment and none had moderate cognitive impairment.

Follow up data on mania, depression and cognition has been mentioned in table 6.

Table 6: Clinical scores at follow up

S No	Characteristics	Value (N = 51) n (%) / Median (IQR) / Mean ± SD
1.	Mania: Median YMRS score	0
2.	Depression: Median HAM D score	0
3.	Cognition: Median COBRA score	1.5 (IQR: 0-6)
4.	Cognition: Median MoCA score	27 (IQR: 26-28.25)

4. Outcome assessment:

4.1Primary Outcome:

4.1.1.1 On assessing the baseline and follow up data of participants with bipolar disorder 1 in order to evaluate the effectiveness of pharmacological treatment on cognition, a change in median score of cognition was seen on the COBRA and MoCA scales **(Figure 9).** On the COBRA scale, a median score of 06 (IQR: 1-12) at baseline decreased to 1.5 (IQR: 0-6) suggesting improvement in median score of cognition and on applying the Wilcoxon signed rank test, a statistically significant difference was seen ($p<0.05$).

While assessing on the MoCA scale, a median score of 25 (IQR: 20-28) at baseline increased to 27 (IQR:26-28.25) suggesting improvement in median score of cognition and on applying Wilcoxon signed rank test, a statistically significant difference was seen ($p<0.05$). Table 7 shows the statistical analysis for change in cognition.

Table7: Statistical analysis for cognition

Test statistics [a]		
	COBRA Follow up – COBRA baseline	MoCA Follow up – MoCA baseline
Sig. (2-tailed)	.000	.000

a. Wilcoxon Signed Ranks Test

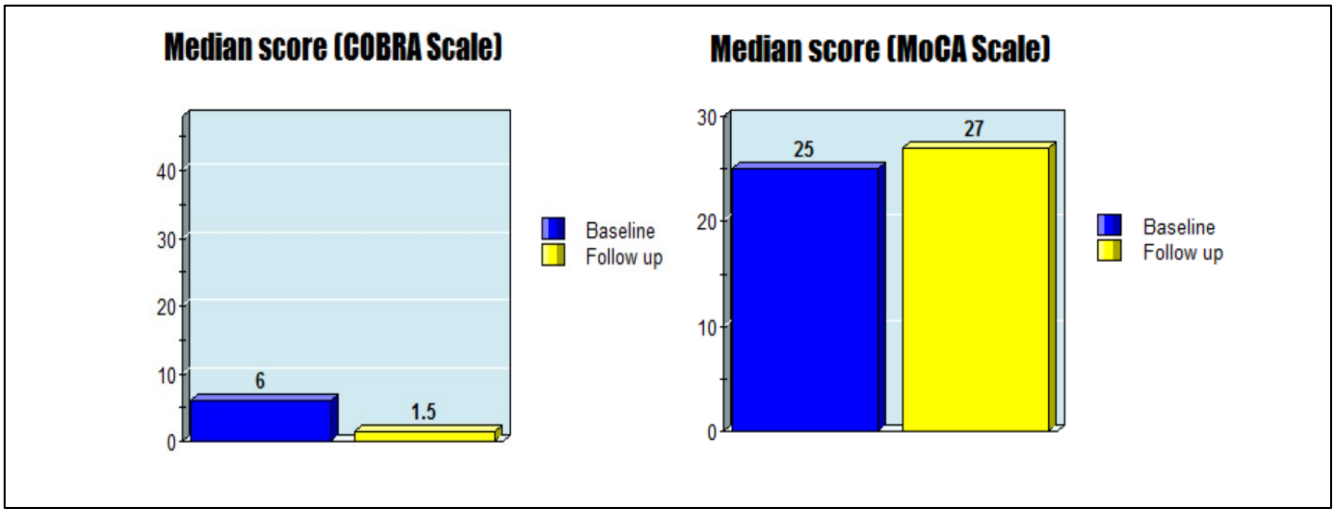


Figure 9: Median score of cognition on COBRA and MoCA scales

- On assessing the change in category of cognition on the COBRA and MoCA scales:

  As per COBRA scale, at baseline, 40 (78.4%) participants had normal cognition and 11 (21.5%) had moderate to severe cognitive impairment. However, at follow up 47 (92.2%) participants had normal cognition and 03 (5.9%) had moderate to severe cognitive impairment suggesting improvement in categories of cognition **(Figure 10)**. On applying the McNemar test, a statistically significant difference was seen ($p<0.05$).

  As per MoCA scale, at baseline, 22 (43.13%) participants had normal cognition, 24 (47.1%) had mild cognitive impairment and 05 (9.8%) had moderate cognitive impairment. However, at follow up 38 (74.5%) participants had normal cognition, 12 (23.5%) had mild cognitive impairment and none had moderate cognitive impairment, suggesting improvement in categories of cognition **(Figure 11)**. On applying the Fisher's exact test, no significant difference was seen in change between the normal cognitive categories between baseline and follow up data ($p = 0.226$). However, a significant difference was seen between the change in cognitive category from moderate to mild ($p = 0.004$) and mild to normal ($p = 0.030$) when follow up data was compared with baseline data. Table 8 shows the statistical

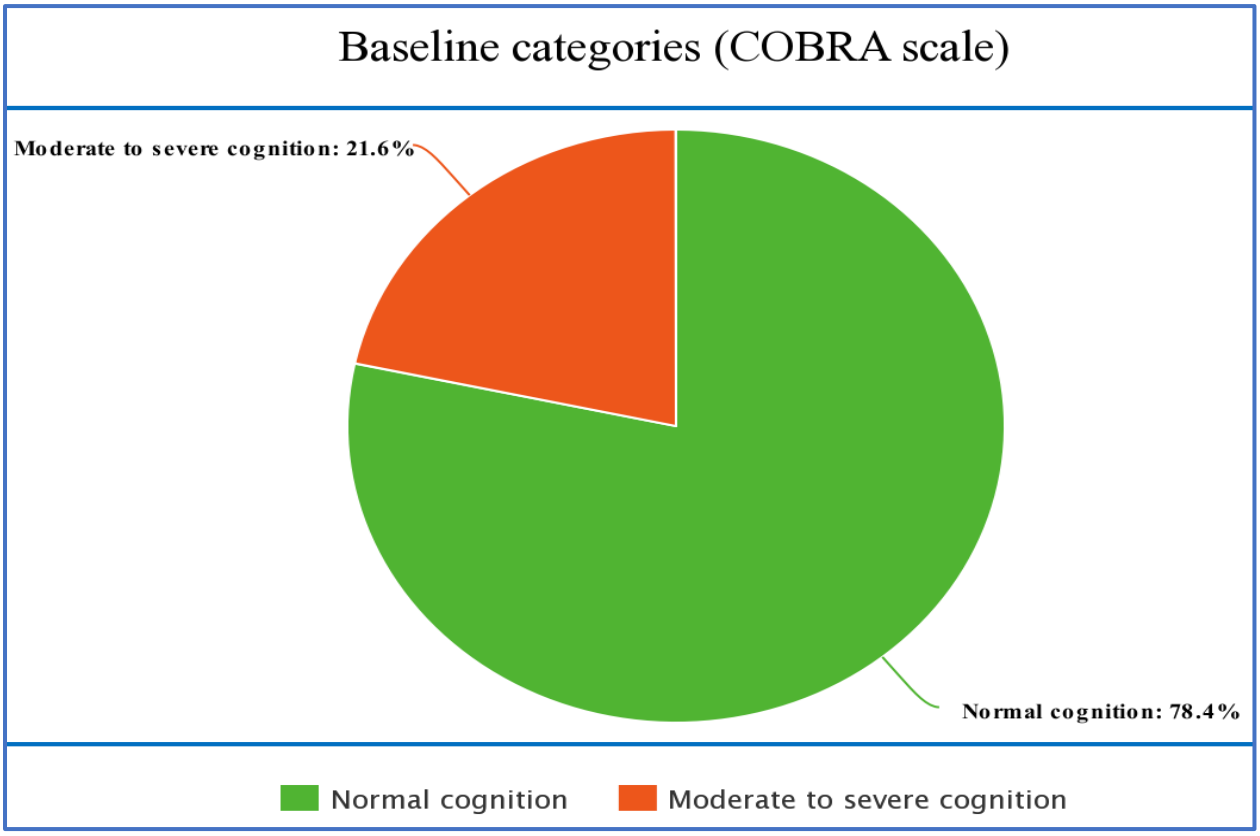
analysis for change in category of cognition on COBRA scale and table 9 shows change in category of cognition on MoCA scale.

Table 8: Statistical analysis for change in category of cognition on COBRA scale

Test Statistics[a]	
	COBRA category at baseline & COBRA category at baseline
N	**50**
Exact Sig. (2-tailed)	**.016**
a. McNemar Test	

Table 9: Statistical analysis for change in category of cognition on MoCA scale

Follow up / Baseline	Normal	Mild	p Value
Normal	19	02	0.226
Mild	17	05	0.004
Moderate	02	05	0.030
Fisher's exact test			



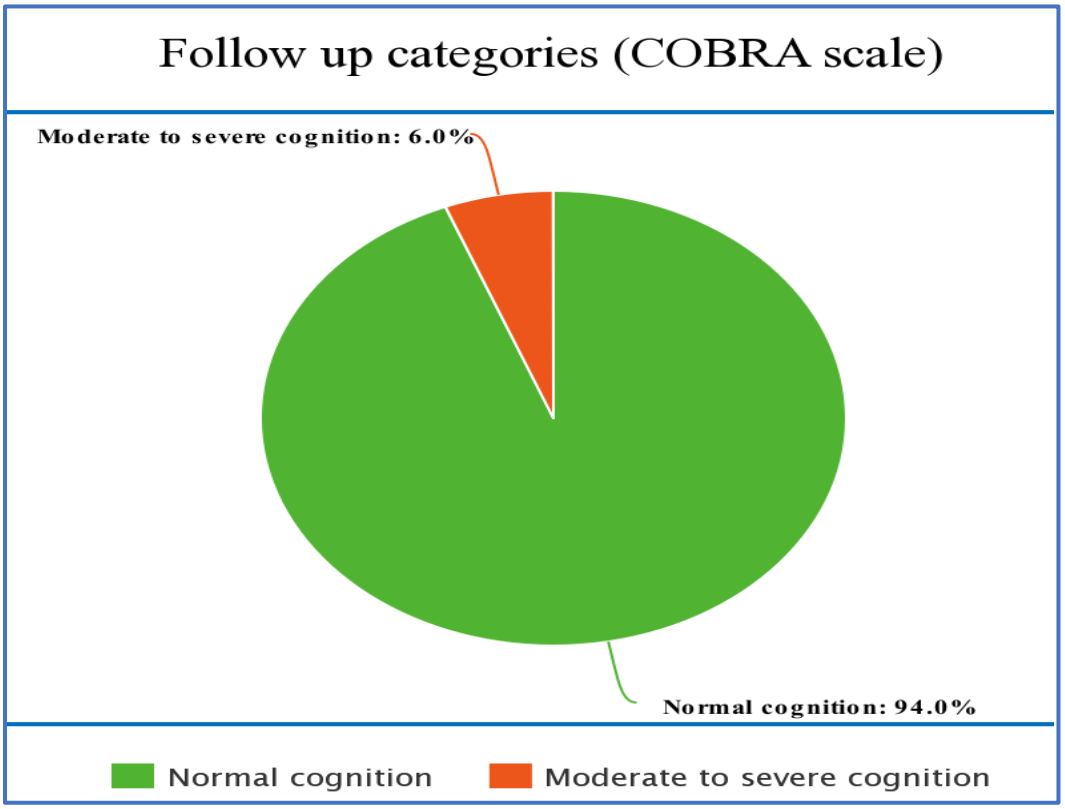
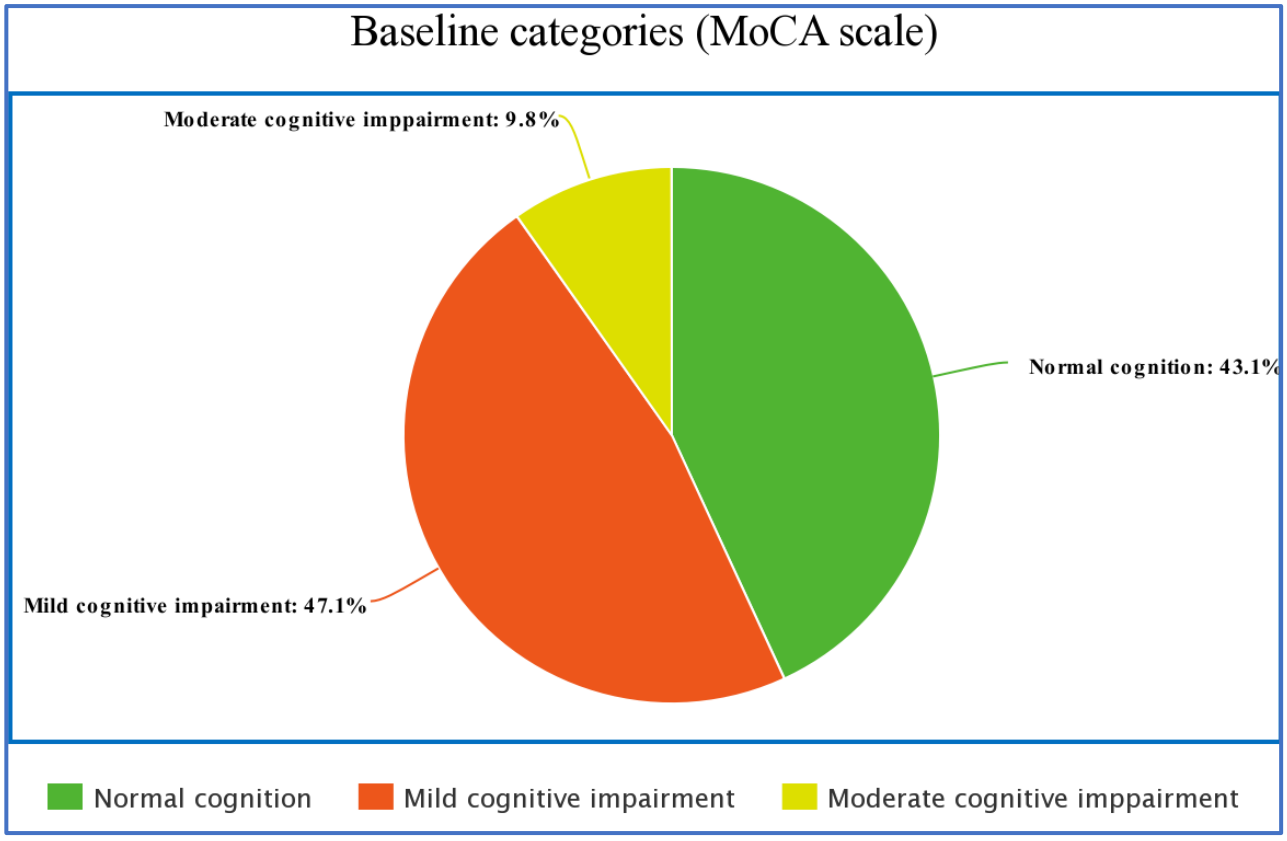


Figure 10: Change in categories of cognition on COBRA scale



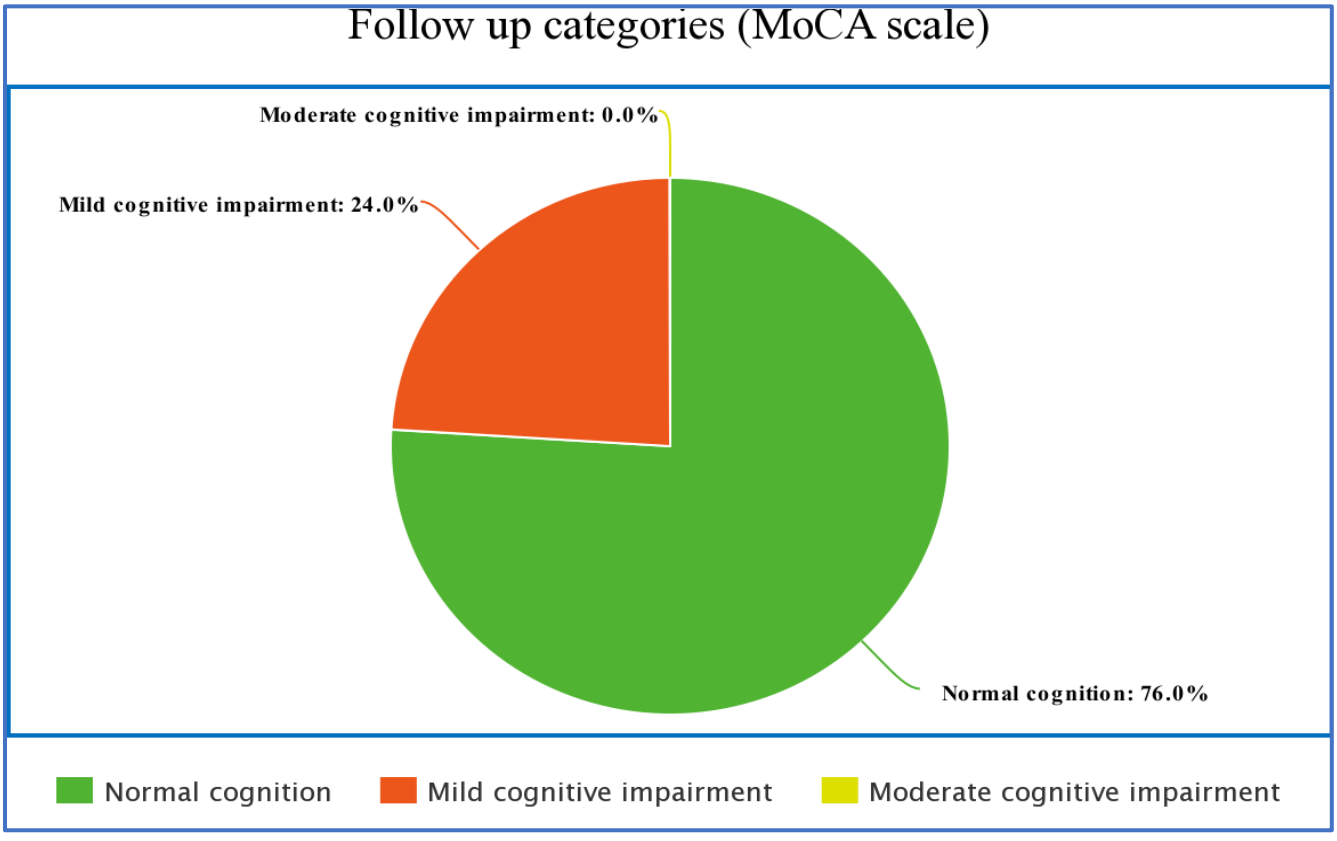


Figure 11: Change in categories of cognition on MoCA scale

4.1.2 Correlation:

On analysing various baseline characteristics of the participants with the cognitive scores obtained on the COBRA and MoCA scales, no significant correlation was seen ($p<0.05$), on applying appropriate correlation methods (Spearman correlation or Point biserial correlation) Table 10 shows the correlation of baseline characteristics and cognition.

Table 10: Correlation between Baseline characteristics and cognition

S No.	Cognition / Characteristics	COBRA score (p value)	MoCA score (p value)
1.	Age	0.25[a]	0.13[a]
2.	Gender	0.69[b]	0.09[b]
3.	Duration of illness	0.25[a]	0.13[a]
4.	Level of education	0.49[a]	0.13[a]
5.	Family history	0.06[a]	0.59[b]
6.	Suicidal thought	0.33[b]	0.69[b]
7.	Suicidal attempt	0.67[b]	0.86[b]
8.	Smoking	0.14[b]	0.69[b]
9.	Alcohol intake	0.79[b]	0.67[b]
10.	Co-morbidities	0.60[b]	0.19[b]

a: Spearman correlation
b: Point biserial correlation

4.1.3 Sub group analysis:

We did a sub group analysis of the drug/drug regime prescribed to more than five participants. 11 participants were prescribed with divalproex sodium followed by 10 participants on anti-psychotics, 08 on combination of divalproex sodium and olanzapine, 07 on combination of lithium carbonate and olanzapine. A change in median score was seen from baseline at follow up on both the scales measuring cognition, namely, COBRA and MoCA scales, suggesting

improvement in cognition. However, a statistically significant difference was seen only with divalproex sodium and anti-psychotics on both the scales, and with divalproex sodium and olanzapine on MoCA scale ($p<0.05$). On applying the Freidman test, no significant difference in median values were obtained between the groups on COBRA scale ($p = 0.901$) but a significant difference was seen on MoCA scale ($p = 0.018$). On applying the post hoc test (Related-Samples Friedman's Two-Way Analysis of Variance by Ranks) for MoCA scale, a significant difference was seen between divalproex sodium and lithium carbonate + olanzapine groups ($p = 0.043$). Table 11 shows the sub group analysis for cognition

Table 11: Sub group analysis of drug/drug regime with cognition

S No.	Drug/Drug regime	COBRA Median (IQR)			MoCA Median (IQR)		
		Baseline	Follow up	p Value	Baseline	Follow up	p Value
1.	Divalproex sodium	02 (02-06)	0 (0-1)	0.020	24 (24-27)	27 (27-29)	0.012
2.	Anti-psychotics	06 (01-15)	01 (0-07)	0.043	27 (23-28)	27 (26-28)	0.026
3.	Divalproex sodium + olanzapine	07 (2.5-9.5)	4.5 (2.5-9.5)	0.167	24.5 (17-26.5)	27 (21.5-29.5)	0.018
4.	Lithium carbonate + olanzapine	05 (02-17)	05 (03-07)	0.068	25 (15-30)	27 (17-27)	0.458

4.2. Secondary outcomes:

4.2.1 Safety reporting:

Out of the total 50 participants who attended the follow up visit, adverse events (AEs) were reported in 28 (54.9 %) participants, who reported a total of 55 AEs; median number of AEs reported per participant was 1 (IQR: 0-1). On assessing AEs as per Hartwig's severity assessment scale all the AEs were of mild type reaction with severity level 1, suggesting no change in treatment was required with the suspected drug. The distribution of the type and severity of AEs reported is displayed and compared in **table 10** using Hartwig's severity assessment scale. Most commonly reported AEs was weight gain (n = 15, 27.2%) with a mean gain in weight of 3.78 kgs (SD: ± 2.51) followed by tremors (n = 12, 21.8%), and drowsiness (n = 8, 14.5%). Other AEs reported were increased thirst and polyuria, dry mouth, postural hypotension, nausea and constipation **(Figure 12)**.

Table 12: Type and severity of adverse events reported is displayed and compared using Hartwig's severity assessment scale.

S No.	Adverse event	n (%) (N=55)	Type of ADR	Severity of ADR (1-7)
1.	Weight gain	(n =15, 27.2%)	Mild	01
2.	Tremors	(n =12, 21.8%)	Mild	01
3.	Increased thirst and polyuria	(n = 09, 17.3%)	Mild	01
4.	Drowsiness	(n = 08, 15.4%)	Mild	01
5.	Dry mouth	(n = 08, 15.4%)	Mild	01
6.	Postural hypotension	(n= 01, 0.0%)	Mild	01
7.	Nausea	(n= 01, 0.0%)	Mild	01
8.	Constipation	(n= 01, 0.0%)	Mild	01

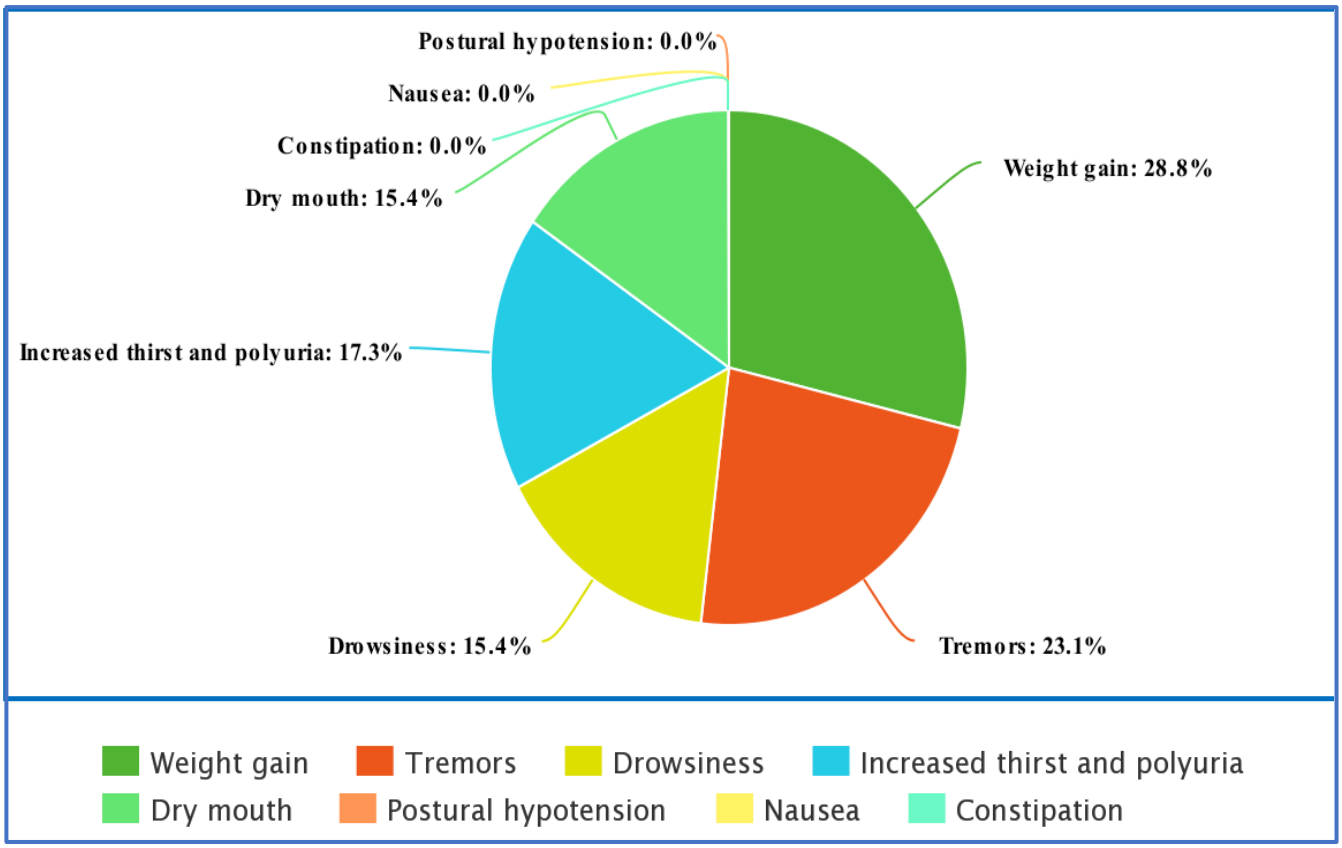


Figure 12: Adverse events with their frequencies

4.2.2 Causality analysis of these reported AEs was done using the WHO UMC scale, after they were reported to the AMC operating in the institute in the department of Pharmacology. It showed that all 52 (94.5%) adverse events fell under the category of possible and 03 (5.4%) fell under the category of unlikely as per WHO-UMC assessment scale. Table 11 shows the different adverse events seen in the participants with the drugs they were prescribed. Table 12 shows the adverse events with their causality assessment as per WHO-UMC scale.

Table 13: Adverse events seen in the participants with the drugs they were prescribed

S No.	Adverse event (n=number of events/%=percentage of events)	Drugs prescribed with their frequencies
1.	Weight gain (n =15, 27.2%)	• Divalproex sodium + Olanzapine **(4)**

		• Lithium carbonate + Olanzapine **(3)** • Divalproex sodium **(3)** • Lithium carbonate, Quetiapine, aripiprazole, Lithium carbonate divalproex sodium + aripiprazole, Lithium carbonate + aripiprazole **(1 each)**
2.	Tremors (n =12, 21.8%)	• Lithium carbonate **(2)** • Quetiapine **(2)** • Lithium carbonate + Olanzapine, Lithium carbonate, Divalproex sodium + aripiprazole, divalproex sodium + olanzapine, Divalproex sodium, olanzapine, Lithium carbonate + olanzapine + fluoxetine **(1 each)**
3.	Increased thirst and polyuria (n=9, 17.3%)	• Divalproex sodium + olanzapine **(2)** • Divalproex sodium, Quetiapine, Lithium carbonate + olanzapine + fluoxetine, Lithium carbonate + olanzapine, Lithium carbonate + divalproex sodium + aripiprazole, lithium carbonate + quetiapine, Lithium carbonate **(1 each)**
4.	Drowsiness (n = 8, 15.4%)	• Divalproex sodium + olanzapine **(2)** • Lithium carbonate + olanzapine + divalproex sodium, Lithium carbonate + olanzapine, Divalproex sodium + fluoxetine + quetiapine, lithium carbonate + quetiapine, Lithium carbonate, Quetiapine **(1 each)**
5.	Dry mouth (n = 8, 15.4%)	• Lithium carbonate **(2)** • Divalproex sodium + olanzapine **(2)**

		• Lithium carbonate + olanzapine, Divalproex sodium, Quetiapine, Lithium carbonate + olanzapine + divalproex sodium **(1 each)**
6.	Postural hypotension (n=1, 0.0%)	Divalproex sodium + Fluoxetine + Quetiapine
7.	Nausea (n=1, 0.0%)	Divalproex sodium
8.	Constipation (n=1, 0.0%)	Divalproex sodium + olanzapine

Table 14: **Adverse events with their causality assessment as per WHO-UMC scale**

S. No.	Causality category	Number of Adverse events(n)	Percentage (%)
1	Certain	0	0
2	Probable	0	0
3	Possible	**52**	**94.5%**
4	Unlikely	**03**	**5.5%**
5	Conditional/unclassified	0	0
6	Unassessable/unclassifiable	0	0
Total		**55**	**100**

4.2.3 Medication adherence:

On applying the Medication adherence rating scale (MARS) on the participants of bipolar disorder 1, a median score of 10 (IQR: 08-10) was achieved, suggesting good adherence towards the pharmacological treatment amongst the participants.

4.2.4 Prescription pattern analysis:

Prescription pattern of drugs used in the participants of bipolar disorder 1 were characterized to comprehend the pattern of drug usage. Amongst all the classes of drugs, mood stabilizers were the maximum prescribed class, (n=16, 31.3%) and amongst different drug regimen divalproex sodium was the maximum prescribed drug, (n=11, 21.5%). **Figure 13** shows different drug and drug regimens prescribed with their relative distribution.

All the drug and drug regimen were given by oral route for a duration of 3-4 months and at follow up, none of the drug was withdrawn or replaced nor any dose adjustment was done.

Table 13 shows the pharmacotherapy details of the prescribed drug and drug regimen.

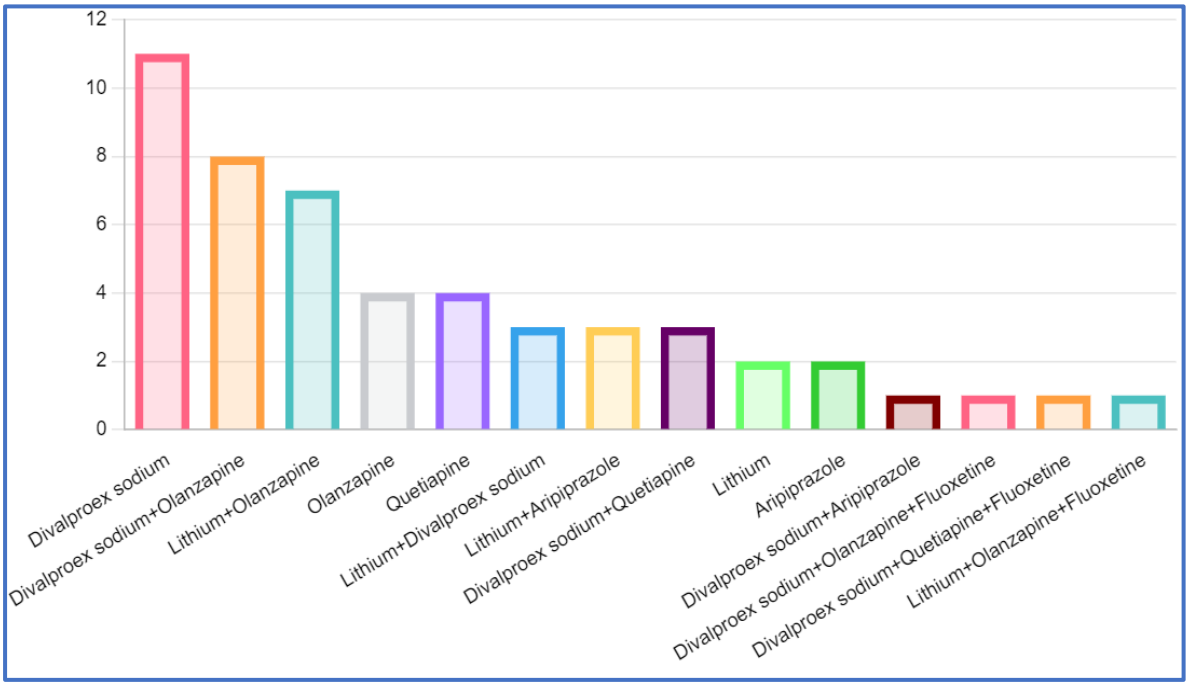


Figure 13: Drugs prescribed with their relative distribution

Table 15: Pharmacotherapy details of the drugs prescribed for bipolar disorder 1

S No.	Drug prescribed with composition	No of participants	Dose form	Dose (mg)	Dosage frequency	Frequency of prescription
1.	Lithium carbonate	02	Tablet	300	OD	01

				600	OD	01
2.	Divalproex sodium	11	Tablet	500	OD	05
				750	OD	04
				1000	OD	02
3.	Lithium carbonate + Divalproex sodium	03	Tablet	300 + 10	OD	01
				800 + 10	OD	01
				600 + 7.5	OD	01
4.	Olanzapine	04	Tablet	10	OD	04
5.	Quetiapine	04	Tablet	400	OD	04
6.	Aripiprazole	02	Tablet	10	OD	01
				15	OD	01
7.	Lithium carbonate + olanzapine	07	Tablet	900 + 10	OD	02
				800 + 10	OD	02
				400 + 10	OD	02
				300 + 10	OD	02
8.	Lithium + aripiprazole	03	Tablet	400 + 10	OD	03
9.	Divalproex sodium + olanzapine:	08	Tablet	100 + 10	OD	01
				750 + 7.5	OD	01
				500 + 10	OD	06
10.	Divalproex sodium + quetiapine	03	Tablet	500 + 400	OD	04

11.	Divalproex sodium + aripiprazole:	01	Tablet	500 + 10	OD	01
12.	Divalproex sodium+ olanzapine + fluoxetine:	01	Tablet	500 + 10 + 40	OD	01
13.	Divalproex sodium + quetiapine + fluoxetine:	01	Tablet	500 + 300 + 20	OD	01
*OD: once daily **BD: twice daily						

5. Results of questionnaire (Hindi translation of COBRA) validation:

A total of 50 subjects (25 participants with bipolar disorder and 25 healthy controls) were included in this validation study. Of the total 25 healthy controls, there were 13 (52%) male and 12 (48%) female participants. Amongst the participants with bipolar disorder there were 16 (64%) male and 9 (36%) female participants. The mean age was 36.16 years (SD: ±7.38 years) in the healthy control group and 32.04 years (SD: ±11.61 years).

5.1 Reliability analysis:

The internal consistency coefficient obtained was high, with Cronbach's alpha=0.749 for the total 16-item scale, suggesting that the items are sufficiently homogeneous. On applying test–retest reliability, the results showed an appropriate stability in the evaluations of patient when analysis was done between the baseline and follow up scores 2 weeks apart, while achieving an intra class corelation coefficient of 0.956.

5.2 Validity analysis:

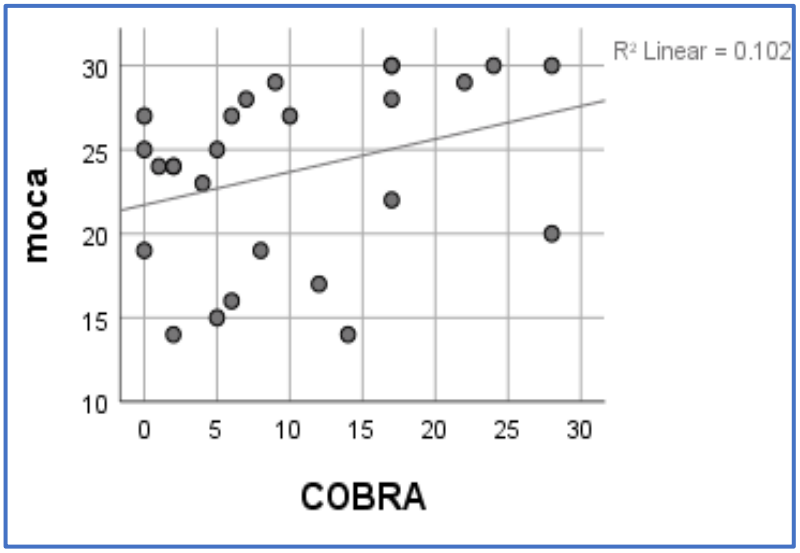
5.2.1 Concurrent validity:

To measure the concurrent validity, spearman correlations were performed to assess the relationship between COBRA and MoCA scores.

5.2.2 Association between COBRA and MoCA scale:

A significant association was seen between the COBRA and the total MoCA score (r_s= 0.398 and P=0.044) **Figure 14**. No association was found between COBRA scores and individual cognitive domains of MoCA scale (p>0.05).

Figure 14: Scatter plot showing association between COBRA and MoCA scale



5.2.3 Discriminative validity:

To detect differences between bipolar participants and healthy controls discriminative validity was done and it was found that participants with bipolar disorder showed higher COBRA total scores (mean=10.44; SD=8.75) than healthy controls (mean=6.56; SD=3.83). Also, a significant difference was seen between the two groups (t= 2.050, P=0.046) **Figure 15.**

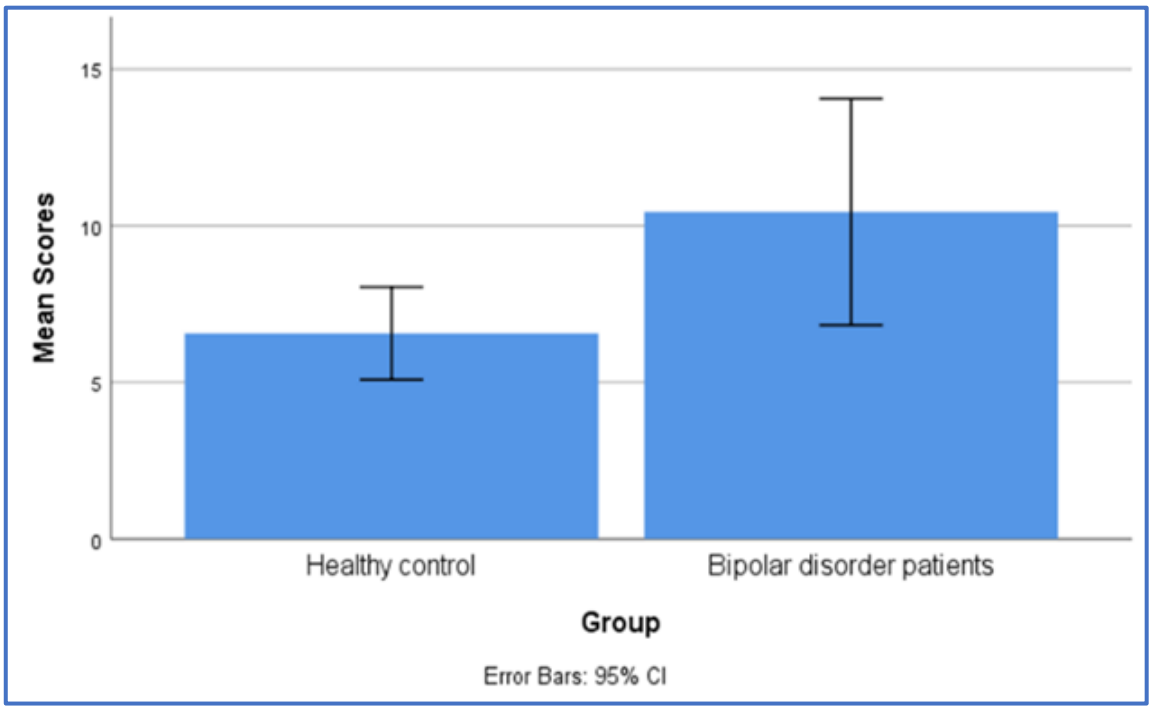


Figure 15: Bar graph showing COBRA scores in healthy controls and bipolar disorder patients

5.2.4 Receiver operating characteristic (ROC) curve:

We analysed the scale's ability to discriminate between patients and healthy controls by means of the diagnostic performance or ROC curve. The area under the curve (AUC) was 01 indicating a good capacity **(Figure 15)**. The discriminative capacity analysis indicated that a score of 15.5 obtains the best balance between sensitivity (100 %) and specificity (100%).

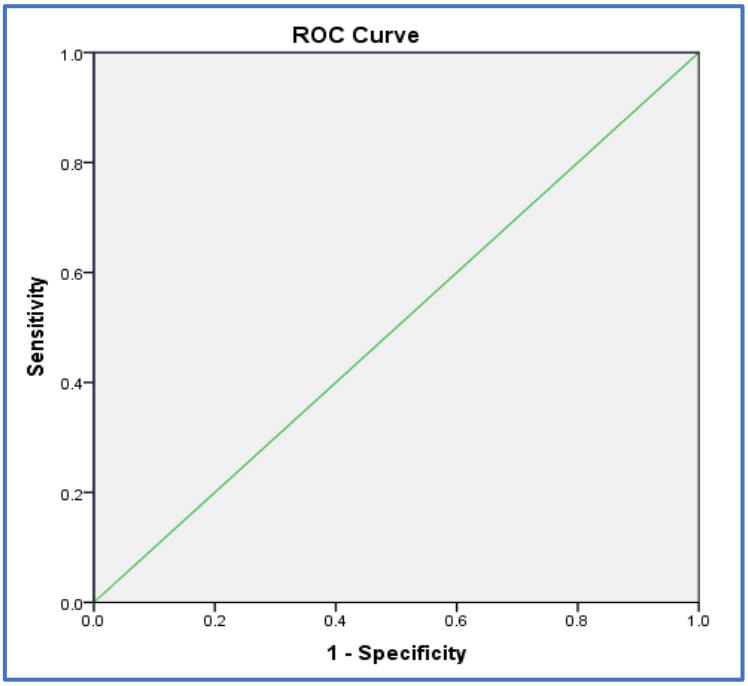


Figure 15: ROC curve

5.2.5 Feasibility:

Finally, the results showed a high feasibility of the Hindi COBRA scale, since the participants answered all the 16 items of the instrument.

Discussion

DISCUSSION

The study was conducted at the Psychiatry OPD of AIIMS Bhopal with the collaboration of Department of Pharmacology and Department of Psychiatry. The study duration was from March 2022 to October 2023 which included initial 3-4 months of validation of Hindi translated COBRA questionnaire used for assessing cognition followed by a year of data collection and 2-3 months of data analysis and thesis compilation. Patients who were euthymic and diagnosed with bipolar disorder 1 were included in the study after applying the inclusion and exclusion criteria. A total of 51 participants were recruited in the study after taking their informed verbal and written consent.

Bipolar disorder is a chronic mood disorder affecting 40 million people worldwide, forming a significant cause of disability. [1] It is also the 16th leading cause of years lost to disability (YLD) worldwide according to the Global Burden of Disease Study, accounting for 9.9 million YLD. As it is the 6th -leading cause of disability-adjusted life years among people aged 10 to 24 years worldwide, its effects on young people are considerably more profound. [2] In India, according to the estimates, bipolar disorder contributed 6.9% (4.9%–9.6%) of all DALYs. [3]

The severity of mood elevation experienced during acute episodes essentially determines the diagnostic subgroups that make up the spectrum of bipolar disorder. During presence of threshold manic episodes, there are characteristics such as inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risky behaviour. This results in a significant functional impairment and may also have psychotic features and/or require hospitalisation. Hence, bipolar disorder 1 is positioned at one pole of this spectrum. To diagnose BPD 1, one episode of mania in the lifetime is compulsory and maybe preceded by or followed by a hypomanic or major depressive episode. [2]

Cognitive impairment, a general term for deficiencies in the mental action or process of obtaining knowledge and understanding through thought, experience, and senses, is one of the

main disabilities of bipolar disorder. This cognitive impairment thus forms an important area to be studied upon. There are findings which consistently demonstrate significant deterioration in the areas of verbal memory, attention, language, and executive function in manic, depressive, and mixed states. [8] The presence and severity of cognitive deficits vary more among euthymic patients. According to estimates, 29–48% of people have no cognitive impairment, 12–40% have specific abnormalities in verbal learning, working memory, and executive function, and 12–40% have impairments throughout all cognitive domains. [39]. It is less obvious to what extent this is a result of the illness or of the treatment. [8] Hence, the primary objective of this study was to evaluate the effect of pharmacological treatment on cognition in patients with bipolar disorder 1 along with other objectives such as assessing the severity and causality of the adverse events reported, to assess the adherence to the medications and prescription pattern analysis.

Baseline characteristics of participants

The median age of participants in the study was 39 years (IQR: 23-49 years) and 29.4% of the participants fell under the age group of 18-25 years and 70.6% were greater than 25 years. Median age of onset of bipolar disorder 1 was 27 years (IQR: 20-38 years). It is unclear how cognitive performance changes over the course of adulthood in BPD. Few research has looked longitudinally or cross-sectionally at cognitive abnormalities in BPD across the age spectrum. It has been seen that ageing is associated with decreased performance on neuropsychological tests in bipolar disorder. [40] In a study done by Lewandowski et al, when compared to adults without psychiatric illness, they concluded that, patients with bipolar disorder have lower cognitive functioning across all dimensions and as they get older, their processing speed may become even more dysfunctional. [40] Cognitive deficits in elderly people with BPD could be due to different mechanisms. The impact of repeated mood episodes, medical comorbidity, substance use/iatrogenic effects, or ageing, in addition to genetic (or possibly

neurodevelopmental) problems, can result in cognitive deficiencies later in life. The brain tissue of individuals with bipolar disorder may be more susceptible to toxic, metabolic, and ischemic insults throughout adult life. On postmortem investigations, a decrease in glial cell throughout the brain tissue of these patients has been seen. In turn, a decreased brain reserve linked to bipolar disorder would manifest as lower cognitive performance as people age. [41]

However, in this study no correlation was established between increasing age and cognitive scores ($p = 0.254$ and $p = 0.130$) on COBRA and MoCA scales respectively. The probable reason behind this could be the small sample size and even smaller sub groups.

Cognitive decline in BPD patients during the euthymic stage can be due to various factors; residual symptoms, frequency and intensity of manic or depressive episodes in the past, age of onset, presence of any co-morbidities, presence of any family history, educational status and the treatment of the patient. Few studies claimed that cognitive skills deteriorated with increase in duration of illness, [31] [42] whereas other study found no correlation between duration of illness and decreased cognitive performance. [43] In this study, we found no correlation between duration of illness and cognitive scores assessed with COBRA ($p=0.25$) and MoCA ($p=0.13$) scales.

Numerous studies have shown the importance of education in determining outcomes related to cognition in later life. The Cognitive 'reserve' (CR) theory was put forth by researchers, and it contends that individuals with higher reserves are able to tolerate better the effects of ageing and associated diseases and cognitive impairment. Reserve often refers to experiences that challenge the mind over the course of a lifetime. Consequently, the level of schooling and employment were frequently utilised as proxies for cognitive reserve. [44] Higher educated individuals typically live longer, have better overall health, and experience fewer morbidities throughout the course of their lives. [45] However, there have been varied results. In a study done by Chen et al. it was seen that higher education acted as a protective factor against ageing, which in turn

assisted in delaying potential cognitive impairment in later life. [45] On the other hand, several studies have found little to no connection between education and cognitive capacities in later life. [44,46] In this study as well, no correlation was established between the level of education and cognitive impairment on either COBRA ($p = 0.497$) or MoCA ($p = 0.138$) scale. The trajectories of various cognitive domains may be affected differently by education, which is one explanation for these inconsistent findings. For instance, Alley et al. used growth curve modelling to demonstrate that higher levels of schooling hastened verbal memory decline, slowed decline in total global cognition, and were unrelated to decline seen with working memory. [47]

Family history of bipolar disorder has also shown to impact cognition. A complex inheritance form or non-mendelian hereditary mechanisms, such as mitochondrial inheritance and non-imprinting, may play a role in the genetics of bipolar disorder. However, no correlation was established between family history and cognition in this study, ($p = 0.06$ and $p = 0.59$) on COBRA and MoCA scales respectively. The probable reason could be our small sample size of 51, out of which only 05 participants had family history. [48]

Another characteristic which has been seen to have an effect over cognition, is smoking. High rates of smokers are seen in people with psychiatric disorders such as schizophrenia, bipolar disorder, major depressive disorder, attention deficit hyperactivity disorder, and co-occurring substance use disorders. [49] As these psychiatric disorders are associated with various cognitive impairments such as deficits in attention, working memory, and response inhibition functions the cognitive enhancing effects of nicotine may be an important determinant of the initiation and maintenance of smoking in this comorbid population. [50] In this study, only 02 (3.9%) participants were smokers, and due to this small number, no correlation could be established between the smoking status and its effect over cognition ($p = 0.13$, $p = 0.69$) on COBRA and MoCA scales respectively. Another important factor affecting cognition is alcohol consumption.

According to the relationship between brain structure and cognitive function, drinking specifically impairs the frontal lobes and connections to other brain regions as well as the cognitive processes that are normally associated with them. [51] 9.8% of the participants in this study consumed alcohol occasionally and no correlation could be established between alcohol consumption and cognition ($p = 0.79$, $p = 0.67$) on COBRA and MoCA scales respectively.

Co-morbidities such as diabetes mellitus and thyroid disorders can in itself lead to cognitive deficits, or can be an adverse effect of the medication being prescribed leading to cognitive decline. Drugs like lithium has been seen to cause thyroid imbalance and atypical antipsychotic like olanzapine leading to metabolic syndrome. Diabetes causes oxidative stress, poor insulin signalling, and insulin resistance, which all contribute to neuronal degeneration and memory loss. [52] In a study done by Xiao song He et.al., they studied that hippocampal atrophy in hypothyroid patients resulted in memory loss, reduced cerebral blood flow, and worse working memory. [53] In this study, 11.8% participants suffered from co-morbidities such as diabetes mellitus type 2 and hypothyroidism, but no correlation could be established with cognition ($p = 0.60$ and $p = 0.19$) on COBRA and MoCA scales respectively. A small sample size could be the reason for no correlation being established.

In a study done by Marzuk et al. it was seen that individuals with current suicidal ideation significantly underperformed in comparison to patients without suicidal ideation on a number of executive activities when examining the neuropsychological correlates of suicidal ideation. The authors also came to the conclusion that diminished executive function is linked to current suicidal ideation, regardless of prior suicide attempts. [54] In this study, 21.6% participants had suicidal thoughts and 13.7% had attempted suicide, however no correlation could be established in this study. Bipolar disorder patients are supposed to be 20–30 times more likely to commit suicide than the general population. [55] A crucial first step in the prevention of suicide and the creation of focused treatment is the identification of risk factors. Alterations in cognitive

processing and related emotional dysregulation are two important factors that are linked to the increased risk of suicidal behaviour in bipolar disorder. Executive processing speed is crucial for effective emotion control and functional results. [56] As mental flexibility, problem-solving skills, and cognitive regions are all linked to resilience and are influenced by executive functions, there may be an increase in vulnerability for suicidal attempts in the patients and thus cognition forms an important area to be focussed upon.

Pharmacological treatment and cognition

The cognitive performance of individuals with bipolar disorder, notably in the executive function and verbal memory domains, has a more negative impact on employment outcomes and quality of life than the disease's symptoms or sociodemographic characteristics. [57] Therapeutic management needs to concentrate on the assessment of cognition and the impact of these changes on quality of life due to the high prevalence and extent of cognitive impairment in bipolar disorder, the early onset of these deficiencies, and their detrimental impact on the psychosocial and professional development of individuals. Additionally, as pharmacological interventions make up a substantial portion of the current care of bipolar disorder, it is crucial to take the cognitive effects of medication into account. [8]

Hence, in this study, objective was to assess the effect of pharmacological treatment on cognition in euthymic bipolar disorder 1 patients. As more than one drug is mostly prescribed to the patients of BPD, the objective of this study was to assess the effect of the prescribed drug/drug regime in changing cognition from baseline to follow up. In this study, there was a change in median score from 06 (IQR: 1-12) at baseline to 1.5 (IQR: 0-6) at follow up on the COBRA scale and from 25 (IQR: 20-28) at baseline to 27 (IQR:26-28.25) at follow up on the MoCA scale. There was a statistically significant difference ($p<0.05$) seen on both the scales indicative of improvement in cognition. COBRA is a subjective scale which measures verbal learning and memory, executive functionality, attention/concentration, working memory,

processing speed, and mental tracking, while MoCA is an objective scale measuring short term memory, visuospatial abilities, executive function, language, attention, concentration and working memory. Individuals suffering with BPD has varied effect across various domains amongst which executive functioning and verbal learning is seen to be affected the most. [58] However, in this study, we did not compare effect on individual domains, rather than we looked for the overall effect on cognition, with the help of COBRA and MoCA scales, which are designed in such a way that different questions cover various domains.

Executive function has a negative relationship with serum lipid peroxide levels (LPH) in bipolar disorder, which may be controlled by brain-derived neurotrophic factor (BDNF). LPH and BDNF may therefore be helpful indicators for identifying bipolar disorder with impaired executive function. [9] The significance of BDNF is not just across mood phases but also in cognitive functioning. Lower BDNF levels and impaired executive performance in bipolar disorder patients during stable periods or manic episodes was found when compared to healthy volunteers. [59] In a study done by Peyian Ni et al. MsrA gene was seen to be been linked with decreased executive function in bipolar disorder 1 patients in Chinese population and the rs4840463 polymorphism in the MsrA gene was linked to an increased chance of developing BPD 1 in the future. [60]

In a study done by Carla Torrent et al. on “Effects of atypical antipsychotics on neurocognition in euthymic bipolar patients”, they concluded that on comparison with healthy controls, bipolar patients using one of the three antipsychotics, namely olanzapine (n=26), quetiapine (n=12) or risperidone (n=30), a dose-independent significant deficit was seen on cognition. Following many head-to-head group comparisons, the quetiapine-treated patients demonstrated improved verbal fluency, short-term memory, and recognition tasks as measured by the California Verbal Learning Test. [12]

In contrast to their study, we included only patients with bipolar disorder 1 to see the effect of pharmacological treatment (antipsychotic alone or in combination with mood stabilizers) on cognition. 19.6% of the participants were given anti-psychotics alone and 43.1% of the participants were given a combination of mood stabilizer and anti-psychotic. On subgroup analysis of effect of anti-psychotic on cognition when given alone, there was a significant change on both the COBRA and MoCA scales, indicative of improved cognition. A detailed analysis regarding individual anti-psychotic could not be done pertaining to small sample size and also as drugs were given mostly in combination instead of being prescribed alone. Amongst the anti-psychotics, olanzapine (n=4) and quetiapine (n=4) were prescribed maximally in this study. In another study done by Shi et al, an improvement in cognitive domains was seen by action on dopaminergic pathways leading to improvement in psychotic symptoms and thus an improvement in cognition. [61]

Cognitive impairment has been seen with valproate and the postulated mechanism behind this is the decreased neuronal excitability leading to cognitive impairment. [62] Although in this study, on subgroup analysis a significant improvement in cognition was seen in patients with valproate when prescribed alone. This could be due to its neuroprotective action or stable phase of the disorder. In vitro studies have shown that administration of valproate prevents neuronal mortality in rat cultured neurons against glutamate-induced excitotoxicity and in hippocampal slice cultures exposed to oxygen-glucose deprivation. [63] On sub group analysis to assess the effect of valproate with olanzapine on cognition, a median change in baseline score on follow up was seen with the cognitive scales. A significant difference was found on the MoCA scale but no significant difference was observed with COBRA scale ($p>0.05$). This difference between the two scales could be because of the subjective nature of COBRA scale in comparison to the objective nature of MoCA scale. This also could be due to residual symptoms of the past psychotic episode, for which the patient had been started on anti-psychotic and thus a longer

duration of follow up with a large sample size can be conducted to further explore the effect of valproate alone or in combination.

Lithium is one of the mood stabilizers which is often prescribed to the patients with bipolar disorder. According to a meta-analysis of 12 studies on the drug in both healthy participants and people with mood disorders, lithium showed a small detrimental effect on cognitive performance only in the areas of verbal learning, memory, and creativity. [64] In this study, lithium was maximally prescribed in combination with olanzapine, rather than alone and an improvement in median score was observed on both the scales but there was no significant difference. In contrast to our finding, another study concluded that, attention, memory, and the majority of executive skills is preserved better in people using lithium compared to those receiving treatment with other mood-stabilizing medications. [62] However, there assessment of cognition was done on 15 euthymic bipolar disorder 1 patients solely on lithium for a period of 12 months. Our findings were different as in this study we did a sub group analysis of effect of combination regime of lithium with olanzapine on cognition after 3-4 months. Greater understanding of the same can be obtained from studies with greater sample sizes and long duration of follow up.

Prescription pattern

As different medications might affect cognition differently, we conducted an observational study to determine how the pharmacological therapy as a whole affected cognition rather than simply analysing the drug in isolation. This is because drugs are usually given in combination in accordance with various recommendations. Different classes of drugs were prescribed to the participants: 16 (31.3%) were on mood stabilisers, 10 (19.6%) were on anti-psychotics, 22 (43.1%) were on a combination of a mood stabiliser and an anti-psychotic, and 3 (5.88%) were taking a mood stabiliser, an anti-psychotic, and an anti-depressant. Mood stabilisers were the most commonly prescribed class overall, while divalproex sodium was the most commonly

prescribed drug type overall (n=11, 21.5%). Different guidelines available such as American Psychiatric Association 2002, National Institute of Health and Care Excellence (NICE) 2014, updated 2020, Canadian network for mood and anxiety treatment (CANMAT) and Internal Society for bipolar Disorder, 2018 and Clinical Practise Guidelines (CPGs), Indian Psychiatric Society (IPS) 2017, suggests use of mood stabilizers, antipsychotics and anti-depressants depending on the phase of disorder, previous treatment history and adverse effect profile. The prescribed medications in this study were in line with the guidelines.

Safety and monitoring:

Before beginning pharmaceutical treatment for bipolar disorder, a thorough medical history should be taken. Patients on maintenance therapy with lithium should have their thyroid, renal, and plasma calcium levels evaluated at 6 months, then at least yearly after that, or as prescribed by the doctor. In patients receiving treatment with valproate, one should get their haematology profile, liver function tests done and also keep a regular check of their menstrual cycle. These should be obtained at 3–6-month intervals during the first year, then once a year after that, moreover, as clinically suggested. Patients on atypical antipsychotics should have their weight checked every three months following the first three months. Fasting blood sugar, lipid profile, and blood pressure should all be checked every three and six months and then annually after that. Regular monitoring and vigilance towards the adverse effects in regard to weight fluctuations and extrapyramidal symptoms are required.[2]

Out of the total 50 participants who attended the follow up visit, 28 (54.9 %) participants presented with adverse events and a total of 55 AEs were reported. Most commonly reported AEs was weight gain (n = 15, 27.2%) with a mean gain in weight of 3.78 kgs (SD: ± 2.51). It was most commonly observed in patients using olanzapine and divalproex sodium together, which is a documented side effect of both medications. Similar to our result, studies have shown an increase in weight (1-5) kgs after 4 weeks of therapy with olanzapine and (1-2) kgs after 3

weeks of therapy with valproate. [65][66] It has been postulated that weight gain in olanzapine is due to the metabolic changes and with valproate due to increase in appetite more than metabolic alterations.

The next common adverse effect was tremors (n = 12, 21.8%). This was most commonly seen with lithium. According to a recent study, the oscillator was likely positioned at the cortical level through a mechanism built into the way the motor system is structured and was transmitted through the corticospinal tract. Due to the association between brain lithium levels and the onset of the tremor and its effects on neuronal plasticity, lithium tremor is thought to originate from the central nervous system. Lithium tremor is manageable for many individuals and frequently gets better on its own over time. After assessing the intensity of tremor, if it is very troublesome, potential aggravating factors like caffeine should be controlled. Whenever possible, strategies such as, lowering the dosage of lithium can be beneficial. Although this should be balanced against keeping the dose at a level which is still effective. Altering the lithium preparation from long acting to short acting, switching to a different salt, such as citrate instead of carbonate, or using divided dosing may also be beneficial. [67] Other common adverse effects seen with various drugs were postural hypotension, drowsiness, dry mouth and constipation.

All the adverse effects seen were of mild in nature with level 1 severity on Hartwig adverse drug reaction scale and thus did not require any change, withdrawal or dose adjustment of the drug.

Medication adherence

Medication adherence is a very important aspect with respect to effective treatment. It depends on various factors such as phase of the disorder, proper awareness provided to the patients in form of counselling regarding the drug and its effect and safety profile of the drug. In this study, all the participants were euthymic and were well counselled. On assessing adherence with the help of MARS questionnaire, a median score of 10 (IQR: 08-10) was achieved indicative of good adherence which can be considered as a contributory factor in improvement of cognition.

Validity of Hindi translation of COBRA questionnaire:

Our findings demonstrated that the Hindi version of COBRA had a good internal consistency and retest reliability, which were sufficient psychometric qualities for usage in patients with bipolar disorder. The considerable variations between patients and controls in the COBRA were evidence of discriminative validity. And as predicted, patients' total COBRA scores were greater than those of healthy controls. Despite the fact that the instrument is a self-report, there is published research on the appropriateness and accuracy of self-assessments or self-report evaluations in patients with mental chronic illness. [68] As a result, the 16-item Hindi version of the COBRA scale appears to be an effective self-administered tool for evaluating cognitive symptoms in Hindi speaking population with bipolar disorder.

SUMMARY:

This prospective observational study was done to evaluate the effect of pharmacological treatment on cognition in patients with bipolar disorder 1. The study was conducted at the psychiatry OPD of AIIMS Bhopal with the collaboration of Department of Pharmacology and Department of Psychiatry, AIIMS Bhopal. A total of 51 euthymic (score ≤7 on Young Mania Rating Scale and ≤10 on Hamilton Depression Rating Scale) participants with bipolar disorder 1 were included in the study. Bipolar disorder is a chronic, debilitating mood disorder affecting 40 million people worldwide and is a significant cause of disability. One major component of this disability is cognitive impairment. Patients presents with cognitive deficits regardless of their phase of illness, even during euthymia. It is unknown if cognitive deficit develops as a result of the disease or the treatment. Effect of pharmacological treatment on cognition is uncertain due to insufficient number of studies and hence this study was conducted. Two cognitive scales COBRA and MoCA were used to assess the cognition at baseline and then at follow up after 3-4 months. A significant change in median score of 06 (IQR: 1-12) at baseline to 1.5 (IQR: 0-6) on COBRA scale and a median score of 25 (IQR: 20-28) at baseline to 27 (IQR:26-28.25) on MoCA scale was seen ($p<0.05$). On comparing change in cognitive categories of both COBRA and MoCA scale from baseline to follow up, it was found that, at baseline, 40 (78.4%) participants had normal cognition and 11 (21.5%) had moderate to severe cognitive impairment. However, at follow up 47 (92.2%) participants had normal cognition and 03 (5.9%) had moderate to severe cognitive impairment suggesting significant improvement in categories of cognition on COBRA scale. As per MoCA scale, at baseline, 22 (43.13%) participants had normal cognition, 24 (47.1%) had mild cognitive impairment and 05 (9.8%) had moderate cognitive impairment. However, at follow up 38 (74.5%) participants had normal cognition, 12 (23.5%) had mild cognitive impairment and none had moderate cognitive impairment, suggesting improvement in categories of cognition. On statistical analysis, no

significant difference was seen in change between the normal cognitive categories (p = 0.226). However, a significant difference was seen between the change in cognitive category from moderate to mild (p = 0.004) and mild to normal (p = 0.030) at follow up. The median prescribed number of drugs to participants were 02 (IQR: 2-3). They were prescribed with different classes of drugs, namely, 16 (31.3%) participants were on mood stabilizers, 10 (19.6%) on anti-psychotics, 22 (43.1%) on a combination of a mood stabilizer and an anti-psychotic and 03 (5.88%) were on a combination of a mood stabilizer, an anti-psychotic and an anti-depressant. On doing subgroup analysis of the drugs prescribed to more than 05 participants, a change in median score was seen at follow up on both the cognitive scales. However, a statistically significant difference was seen only with divalproex sodium and anti-psychotics on both scales, and with divalproex sodium and olanzapine on MoCA scale ($p<0.05$). No significant difference was seen between the groups on COBRA scale (p = 0.901) but was found with MoCA scale (p = 0.018). On post hoc analysis a significant difference was seen between divalproex sodium and lithium carbonate with olanzapine group (p = 0.043). A total of 55 adverse events were reported by 54.9% of the participants. Most commonly reported AE was weight gain (n = 15, 27.2%) with a mean gain in weight of 3.78 kgs (SD: ± 2.51) followed by tremors (n = 12, 21.8%), and drowsiness (n = 8, 14.5%). Other AEs reported were increased thirst and polyuria, dry mouth, postural hypotension, nausea and constipation. All the AEs were of mild type reaction with severity level 1 as per Hartwig's severity assessment scale, suggesting no change in treatment was required with the suspected drug. On doing causality assessment using the WHO UMC scale, all 52 (94.5%) adverse events fell under the category of possible and 03 (5.4%) fell under the category of unlikely. Medication adherence being an integral part of medication effectiveness, was assessed and a median score of 10 (IQR: 08-10) was achieved, suggesting good adherence towards the pharmacological treatment amongst the participants. Apart from assessment of cognition, the other objective of the study was to validate the Hindi translation of

COBRA questionnaire, upon validating a good internal consistency (Cronbach's alpha = 0,749) and retest reliability (ICC = 0.956) was achieved, which were sufficient psychometric qualities for usage in patients with bipolar disorder. The considerable variations between patients and controls in the COBRA were evidence of discriminative validity. And as predicted, patients' total COBRA scores were greater than those of healthy controls. As a result, the 16-item Hindi version of the COBRA scale appears to be an effective self-administered tool for evaluating cognitive symptoms in Hindi speaking population with bipolar disorder.

LIMITATIONS

This was a prospective observational study, so it has all limitations of such a study design. The small sample size was a major limiting factor of the study. Although we had planned to include 60 patients for the primary objective, we were able to recruit only 51 patients. As initial 3-4 months were dedicated to the validation of Hindi translation of COBRA scale used for measuring cognition. Hence, effective data collection was of one year. Since, the patient inflow has decreased since COVID 19 and as our participant recruitment was inclusive of only those patients who were euthymic and diagnosed with bipolar disorder 1, it led to recruitment of 51 participants. The participants could not be followed for a longer duration due to the short duration of the study, it being a dissertation topic and the long-term impact of pharmacological treatment on cognition could not be assessed. Another limitation, was the lack of a predetermined baseline disease duration, which could have affected the cognition although this study did not find any correlation.

CONCLUSIONS

- This prospective observational study was done to evaluate the effect of pharmacological treatment on cognition in patients with bipolar disorder 1.
- The study demonstrates that the Hindi version of COBRA questionnaire is a valid and reliable measure for assessing subjective cognitive complaints in Hindi speaking population with bipolar disorder.
- The study also concludes that pharmacotherapeutic treatment leads to an improvement in cognition which was reflected by significant change of the cognitive scores and improved cognitive categories at follow up on both the COBRA and MoCA scales.
- This study also emphasises on the need of vigilant monitoring of occurrence of adverse event. All the adverse events reported were of mild type with level 1 severity requiring no change or withdrawal or titration of the drug.
- Participants also demonstrated a good adherence towards the medications, which can be considered as a contributory factor in cognitive improvement.

FUTURE SCOPE

Cognitive impairment being an integral part of disability seen in patients with bipolar disorder, further trials and studies need to be conducted. Effect of optimal drug and dosage regime on cognition can be explored. Relationship of plasma concentration of the drug and its effect on cognition can be an interesting area to be studied upon. Bipolar disorder being a chronic disease long duration studies with large sample size and multiple follow ups can be designed to see the long-term effect of pharmacotherapy over cognition. As evidences suggest varying effect of different pharmacotherapeutic agent, a sub group analysis of different drug/drug regime with an adequate sample size can be performed to see the effect on cognition. Apart from this multicentric trials can be done for better research on the same. As genetic traits and polymorphism has shown some evidence in bipolar disorder patients, pharmacogenetic research can be done which may prove to be revolutionary.

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Annexures

अखिल भारतीय आयुर्विज्ञान संस्थान, भोपाल

All India Institute of Medical Sciences, Bhopal

ANNEXURE1

INFORMED CONSENT

Title of research: 'Evaluation of the effect of pharmacological treatment on cognition in patients with bipolar disorder-1- A prospective observational study.'

I_____s/o/d/o_____age_____years, a resident of_____ being in sound mind and judgement, do hereby give my consent for participating in the above mentioned study.

• I have been clearly explained and informed about the study in my own language.

• I am fully aware of the fact that my participation in this study is completely voluntary and wilful and I can withdraw from the study at any point of time.

• I am assured that withdrawal from the study will in no way affect the ongoing treatment at AIIMS, Bhopal.

• I will not be paid any remuneration for taking part in this study.

• I will not be required to provide any blood or any other biological sample or undergo any invasive procedure for the purpose of this study.

• I fully understand that the research is being conducted for the benefit of mankind through gain of scientific knowledge and I may not be directly benefitted from this study.

• I will allow the researchers to follow my condition and retrieve parameters like weight, height, x-ray finding, and blood reports. Neither my identity nor the data will be shared with a third party. Only researchers and scientists who will ethically use such information will have access to the collected data.

1. Name of the participant: _____
2. Signature/ left thumb impression of the participant: _____
3. Name of witness: _____
4. Signature/ left thumb impression of the witness: _____
5. Name of the investigator: _____
6. Signature of the investigator: _____
7. Date: _____

अखिल भारतीय आयुर्विज्ञान संस्थान, भोपाल

All India Institute of Medical Sciences, Bhopal

ANNEXURE 2

<u>सूचित सहमति पत्र</u> (INFORMED CONSENT)

<u>शोध का शीर्षक</u>: द्विध्रुवी विकार -1 (Bipolar Disorder-I) के रोगियों में अनुभूति पर औषधीय उपचार के प्रभाव का मूल्यांकन करने के लिए एक संभावित अवलोकन संबंधी अध्ययन।

मैं_____पुत्र/पत्री/पति_____ आयु_____वर्ष, _____ के निवासी, अपने पूरे होश-ओ-आवाज़ में उपरोक्त अध्ययन में भाग लेने के लिए मेरी सहमति देता/देती हूँ ।

• मुझे अपनी भाषा में अध्ययन के बारे में स्पष्ट रूप से समझाया और सूचित किया गया है।

• मैं इस तथ्य से पूरी तरह अवगत हूं कि इस अध्ययन में मेरी भागीदारी पूरी तरह से स्वैच्छिक और स्वेच्छा से है और मैं किसी भी समय इस अध्ययन से हट सकता/सकती हूं।

•मुझे विश्वास है कि अध्ययन से नाम वापस लेने से एम्स, भोपाल में चल रहे मेरे उपचार पर कोई प्रभाव नहीं पड़ेगा।

• इस अध्ययन में भाग लेने के लिए मुझे कोई पारिश्रमिक नहीं दिया जाएगा।

• इस अध्ययन के प्रयोजन के लिए मुझे कोई रक्त या कोई अन्य जैविक नमूना प्रदान करने या किसी आक्रामक प्रक्रिया से गुजरने की आवश्यकता नहीं होगी।

• मैं पूरी तरह से समझता हूं कि वैज्ञानिक ज्ञान प्राप्त करने के माध्यम से मानव जाति के लाभ के लिए अनुसंधान किया जा रहा है और मुझे इस अध्ययन से सीधे लाभ नहीं मिल सकता है।

• मैं शोधकर्ताओं को मेरी स्थिति का पालन करने और वजन, ऊंचाई, एक्स-रे खोज, और रक्त रिपोर्ट जैसे मापदंडों को पुनः प्राप्त करने की अनुमति दूंगा। मेरी पहचान और डेटा किसी तीसरे पक्ष के साथ साझा नही किया जाएगा । केवल शोधकर्ता और वैज्ञानिक जो इस तरह की जानकारी का नैतिक रूप से उपयोग करेंगे, उनके पास एकत्रित डेटा तक पहुंच होगी।

1. प्रतिभागी का नाम: _____

2. प्रतिभागी के हस्ताक्षर/बाएं अंगूठे का निशान: _____

3. गवाह का नाम: _____

4. गवाह के हस्ताक्षर/बाएं अंगूठे का निशान: _____

5. अन्वेषक का नाम: _____

6. अन्वेषक के हस्ताक्षर: _____

7. दिनांक: _____

ANNEXURE 3

Participant Information Sheet

Title of Research: Evaluation of the effect of pharmacological treatment on cognition in patients with bipolar disorder 1- A prospective observational study.

Introduction:

Patients with both maniac and depressive episodes or patients with maniac episodes alone are said to have bipolar disorder. One major component is cognitive impairment, that refers to deficits in the mental action or process of acquiring knowledge and understanding through thought, experience and senses. We are conducting this study to see the effect of pharmacological treatment on cognition.

The study is research for the doctoral thesis by Dr Bhavya, post graduate student of MD Pharmacology, under the guidance of Dr Ajay Shukla, Assistant Professor, Department of Pharmacology, Dr Abhijit R Rozatkar, Additional Professor, Department of Psychiatry and Dr Shubham Atal, Assistant Professor, Department of pharmacology all from AIIMS Bhopal.

I am going to give you information and invite you to be a part of this research. If there is anything you cannot understand, feel free to ask. I will be happy to clarify any issues. You can also contact me at +91-8348192500 for any other information.

1. Why are we asking you to participate in the study?

You are invited to participate in this study because you have bipolar disorder which is known to affect process of acquiring knowledge and understanding through thought, experience and senses (cognitive dysfunction) for which you are being treated and we would like to see the effect of pharmacological treatment over the same.

2. Do I have to be in this study?

You are free to decide to take part in this study. You can say ‘yes’ or ‘no’. Even if you say ‘yes’ now and sign the consent form. You change your mind anytime later and decide not to participate. Your treatment at AIIMS, Bhopal will be in no way affected by your decision.

3. Why is this research study being done?

There is limited data to show effect of pharmacological treatment over process of acquiring knowledge and understanding through thought, experience and senses (cognitive dysfunction). This study will help us in assessing the same.

4. What will happen if I take part in this study? This is an observational study. You will be asked some simple questions regarding your medical history and we will ask you with the help of validated questionnaire. We will keep a record of the various investigation reports available with you. We will only be recording the facts and figures from your ongoing treatment done by your physician. Your physician will follow you regularly for your own benefit. After 3 months another set of records of your

health parameters and investigation reports done for you will be obtained by us during your follow up visit to the physician.

5. How long will I be in the study?

• You will be under this study for a maximum period of 3 months. However, it is very essential that you continue to follow the treatment advised by your physician even after the study period.

6. Does this study involve any risk on my part?

• You will be under the standard treatment regimens/ protocols by your physician. Nothing new or unknown will be done in this study. Only your health parameters and medical investigation reports will be recorded. Hence this study involves less than minimal risk on your part.

7. Are there any benefits for taking part in this study?

• You may not be directly benefitted from the study but the collected data will add to the existing medical information about the management and will definitely be your contribution for the cause of health for all.

8. Are there any costs for participating in this study?

• You are not required to pay any money for participating in this study.

9. Will I be paid any remuneration for participating in this study?

• No, you will not be paid any remuneration for participating in this study.

10. Will my identity be kept confidential?

• Yes, your identity will be completely confidential during and after the study. Only people directly involved in the study will have access to your data.

11. Who can answer my questions about the study?

• You can freely ask questions regarding anything about the study to the investigators.

12. What will be done to the information collected during the study?

• All such information collected during the study will be used for the cause of medical science. The results of the study may be published or may be shared with other researchers who ethically use such information for the benefit of mankind. But your identity will not be revealed at any point.

IMPORTANT: You will receive a copy of this consent form. Please keep it where you can find it easily later on. It will help you to remember what we have discussed today.

Contact details:

Dr Bhavya,
Post Graduate Resident,
Department of Pharmacology, AIIMS, Bhopal.
Phone No: 8348192500, Email: 1195bhavya@gmail.com

ANNEXURE 4

<u>प्रतिभागी सूचना पत्र (PARTICIPANT INFORMATION SHEET)</u>

<u>शोध का शीर्षक</u>: द्विध्रुवी विकार -1 के रोगियों में अनुभूति पर औषधीय उपचार के प्रभाव का मूल्यांकन करने के लिए एक संभावित अवलोकन संबंधी अध्ययन।

परिचय:

उन्मत्त और अवसादग्रस्तता दोनों प्रकरणों वाले रोगियों या अकेले उन्मत्त एपिसोड वाले रोगियों को द्विध्रुवी विकार कहा जाता है। एक प्रमुख घटक संज्ञानात्मक हानि है, जो मानसिक क्रिया या विचार, अनुभव और इंद्रियों के माध्यम से ज्ञान और समझ प्राप्त करने की प्रक्रिया में कमी को दर्शाता है।

हम इस अध्ययन का संचालन अनुभूति पर औषधीय उपचार के प्रभाव को देखने के लिए कर रहे हैं।

एम्स, भोपाल से डॉ. अजय शुक्ला, सहायक प्रोफेसर, फार्माकोलॉजी विभाग, डॉ. अभिजीत आर रोजतकर, अतिरिक्त प्रोफेसर, मनोचिकित्सा विभाग और डॉ शुभम अटल, सहायक प्रोफेसर, औषधि विज्ञान विभाग सभी के मार्गदर्शन में एमडी फार्माकोलॉजी के स्नातकोत्तर छात्र डॉ भव्या द्वारा डॉक्टरेट थीसिस के लिए अध्ययन शोध है।

मैं आपको जानकारी देने जा रहा हूं और आपको इस शोध का हिस्सा बनने के लिए आमंत्रित करता हूं। अगर कुछ ऐसा है जिसे आप नहीं समझ सकते हैं, तो बेझिझक मुझसे पूछें। मुझे किसी भी मुद्दे को स्पष्ट करने में खुशी होगी। किसी अन्य जानकारी के लिए आप मुझसे +91-8348192500 पर भी संपर्क कर सकते हैं।

1. **हम आपको अध्ययन में भाग लेने के लिए क्यों कह रहे हैं**?

आपको इस अध्ययन में भाग लेने के लिए आमंत्रित किया गया है क्योंकि आपको द्विध्रुवी विकार है जो विचार, अनुभव और इंद्रियों (संज्ञानात्मक शिथिलता) के माध्यम से ज्ञान और समझ प्राप्त करने की प्रक्रिया को प्रभावित करने के लिए जाना जाता है जिसके लिए आपका इलाज किया जा रहा है और उसी औषधीय उपचार पर हम इसका प्रभाव देखना चाहेंगे ।

2. **क्या मुझे इस अध्ययन में शामिल होना है?**

आप इस अध्ययन में भाग लेने का निर्णय लेने के लिए स्वतंत्र हैं। आप 'हां' या 'नहीं' कह सकते हैं। भले ही आप अभी 'हां' कहें और सहमति फॉर्म पर हस्ताक्षर करें। आप बाद में कभी भी अपना विचार बदलते हैं और भाग नहीं लेने का निर्णय लेते हैं । एम्स, भोपाल में आपके उपचार पर आपके द्वारा लिये गये निर्णय का कोई प्रभाव नहीं पड़ेगा।

3. **यह शोध अध्ययन क्यों किया जा रहा है?**

विचार, अनुभव और इंद्रियों (संज्ञानात्मक शिथिलता) के माध्यम से ज्ञान और समझ प्राप्त करने की प्रक्रिया पर औषधीय उपचार के प्रभाव को दिखाने के लिए सीमित डेटा है। यह अध्ययन हमें इसका आकलन करने में मदद करेगा।

4. **यदि मैं इस अध्ययन में भाग लेता हूँ तो क्या होगा?**

यह एक अवलोकन अध्ययन है। आपसे आपके चिकित्सा इतिहास के संबंध में कुछ सरल प्रश्न पूछे जाएंगे और हम मान्य प्रश्नावली की सहायता से आपसे पूछेंगे। हम आपके पास उपलब्ध विभिन्न जांच रिपोर्टों का रिकॉर्ड रखेंगे। हम केवल आपके चिकित्सक द्वारा आपके द्वारा किए जा रहे उपचार के तथ्यों और आंकड़ों को रिकॉर्ड करेंगे। आपका चिकित्सक आपके अपने लाभ के लिए नियमित रूप से आपका अनुसरण करेगा। 3 महीने के बाद आपके स्वास्थ्य

मानकों के रिकॉर्ड का एक और सेट और आपके लिए की गई जांच रिपोर्ट चिकित्सक के पास आपकी अनुवर्ती यात्रा के दौरान हमारे द्वारा प्राप्त की जाएगी।

5. **मैं कब तक अध्ययन में रहूंगा?**

आप इस अध्ययन के तहत अधिकतम 3 महीने तक रहेंगे। हालांकि, यह बहुत आवश्यक है कि आप अध्ययन अवधि के बाद भी अपने चिकित्सक द्वारा बताए गए उपचार का पालन करना जारी रखें।

6**. क्या इस अध्ययन में मेरी ओर से कोई जोखिम शामिल है?**

आप अपने चिकित्सक द्वारा मानक उपचार नियमों/प्रोटोकॉल के अधीन होंगे। इस अध्ययन में कुछ भी नया या अज्ञात नहीं किया जाएगा। केवल आपके स्वास्थ्य मापदंडों और चिकित्सा जांच रिपोर्ट को ही दर्ज किया जाएगा। इसलिए इस अध्ययन में आपकी ओर से न्यूनतम से कम जोखिम शामिल है।

7. **क्या इस अध्ययन में भाग लेने के कोई लाभ हैं?**

हो सकता है कि आप सीधे अध्ययन से लाभान्वित न हों, लेकिन एकत्रित डेटा प्रबंधन के बारे में मौजूदा चिकित्सा जानकारी को जोड़ देगा और निश्चित रूप से सभी के लिए स्वास्थ्य के लिए आपका योगदान होगा।

8. **क्या इस अध्ययन में भाग लेने की कोई कीमत है?**

इस अध्ययन में भाग लेने के लिए आपको कोई पैसा देने की आवश्यकता नहीं है।

9. **क्या मुझे इस अध्ययन में भाग लेने के लिए कोई पारिश्रमिक दिया जाएगा?**

नहीं, इस अध्ययन में भाग लेने के लिए आपको कोई पारिश्रमिक नहीं दिया जाएगा।

10**. क्या मेरी पहचान गोपनीय रखी जाएगी?**

हां, अध्ययन के दौरान और बाद में आपकी पहचान पूरी तरह से गोपनीय रखी जाएगी। केवल सीधे अध्ययन में शामिल लोगों के पास आपके डेटा तक पहुंच होगी।

11. **अध्ययन के बारे में मेरे सवालों का जवाब कौन दे सकता है?**

आप जांचकर्ताओं से अध्ययन के बारे में किसी भी चीज़ के संबंध में स्वतंत्र रूप से प्रश्न पूछ सकते हैं।

12. **अध्ययन के दौरान एकत्र की गई जानकारी का क्या किया जाएगा?**

अध्ययन के दौरान एकत्र की गई ऐसी सभी जानकारी का उपयोग चिकित्सा विज्ञान के लिए किया जाएगा। अध्ययन के परिणाम प्रकाशित किए जा सकते हैं या अन्य शोधकर्ताओं के साथ साझा किए जा सकते हैं जो मानव जाति के लाभ के लिए नैतिक रूप से ऐसी जानकारी का उपयोग करते हैं। लेकिन आपकी पहचान किसी भी बिंदु पर उजागर नहीं की जाएगी।

महत्वपूर्ण: आपको इस सहमति फॉर्म की एक प्रति प्राप्त होगी। कृपया इसे वहीं रखें जहां बाद में आपको यह आसानी से मिल जाए। यह आपको याद रखने में मदद करेगा कि हमने आज क्या चर्चा की है।

संपर्क विवरण:
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All India Institute of Medical Sciences, Bhopal

ANNEXURE 5

CASE RECORD FORM

Title- Evaluation of the effect of pharmacological treatment on cognition in patients with bipolar disorder 1- A prospective observational study.

Initials of the patient:	UHID:	Date:
Age/Gender:	Height:	Weight:
Contact no:	Name and Contact no of Relative:	Address:
Diagnosis:	Pulse:	BP:

History of present illness

Age at onset				
Episodes	Maniac	Hypomanic	Depressive	Mixed
Suicidal attempt				
Suicidal thoughts				
Smoking(Y/N)				
Alcohol(Y/N)				
On any medications	Name		Duration	
Scores	Baseline		At follow up (3Month)	
COBRA				
MoCA				
YMRS				
HAM-D				

Past history:

History of psychiatric illness in past and on any medications	History of hospitalization	History of chronic illness and on any medications	Family history (Family tree)

Review of systems:

Central nervous System

Depression (Y/N)	Mania (Y/N)	Seizure /Epilepsy (Y/N)	Dementia (Y/N)	Delirium (Y/N)	Insomnia (Y/N)

	Any Condition	Duration	On any medication with duration	Remarks
Endocrine system				
Cardiovascular system				
Respiratory system				
Renal system				
Gastrointestinal system				
Musculoskeletal system				
Others				

Did you have any adverse event? Y/N	Onset	Progression	Resolution
Drowsiness			
Weight gain			
Postural hypotension			
Dry mouth			
Blurring of vision			
Constipation			

Galactorrhoea			
Nausea			
Vomiting			
Tremors			
Thirst, polyuria			
Motor incoordination			
Hyperreflexia			
Extrapyramidal disturbances • Akathisia			
• Acute dystonia			
• Parkinsonism			
• Neuroleptic malignant syndrome			
Others			

Pharmacotherapy details:

S no.	Date of prescription	Drug prescribed with composition	Dose form	Dose	Dose frequency	Route	Duration	Remark

ANNEXURE 6

COBRA (Cognitive complaints in bipolar disorder rating assessment)

Name: **NHS:** **Date:**

Please answer all question by putting **a circle** around the **correct answer**, or the answer, youthink best describes you.

1. **Do you have difficulties to remember peoples' names?**

0	1	2	3
Never	Sometimes	Often	Always

2. **Do you have difficulties to find objects of daily use (keys, glasses,wristwatch…)?**

0	1	2	3
Never	Sometimes	Often	Always

3. **Do you find it difficult to remember situations that were important to you?**

0	1	2	3
Never	Sometimes	Often	Always

4. **Is it hard for you to place important events in time?**

0	1	2	3
Never	Sometimes	Often	Always

5. **Do you find it hard to concentrate when reading a book or a newspaper?**

0	1	2	3
Never	Sometimes	Often	Always

6. **Do you have problems recalling what you have read or have been toldrecently?**

0	1	2	3
Never	Sometimes	Often	Always

7. **Do you have the feeling that you do not finish what you begin?**

0	1	2	3
Never	Sometimes	Often	Always

8. **Does it take you longer than normal to complete your daily tasks?**

0	1	2	3
Never	Sometimes	Often	Always

9. Have you ever felt disoriented in the street?

0	1	2	3
Never	Sometimes	Often	Always

10. When people remind you of a conversation or a comment you heard, do youget the impression that it is the first time you hear it?

0	1	2	3
Never	Sometimes	Often	Always

11. Is it sometimes difficult for you to find the words to express your ideas?

0	1	2	3
Never	Sometimes	Often	Always

12. Are you easily distracted?

0	1	2	3
Never	Sometimes	Often	Always

13. Do you find it hard to do simple mental calculations?

0	1	2	3
Never	Sometimes	Often	Always

14. Do you get the impression that you cannot follow a conversation?

0	1	2	3
Never	Sometimes	Often	Always

15. Have you noticed that you find it difficult to learn new information?

0	1	2	3
Never	Sometimes	Often	Always

16. Do you struggle to keep focused on a particular task for a long time?

0	1	2	3
Never	Sometimes	Often	Always

.

ANNEXURE 7

COBRA (Cognitive complaints in bipolar disorder rating assessment) Hindi

नाम: **एनएचएस:** **दिनांक:**

कृपया सही जबाब के सामने गोला बनाकर उत्तर दें, या उत्तर जो आपके हिसाब से वर्णन करता है

1. क्या आपको लोगों का नाम याद रखने में कोई कठिनाई महसूस होती है?

0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

2. क्या आपको रोज के उपयोग कि चीज़ें (चाबियाँ, चश्मा, घड़ी ...) खोजने में कठिनाई होती है?

0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

3. क्या आपको जीवन के महत्वपूर्ण परिस्थिती को याद करने में कठिनाई होती है?

0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

4. क्या महत्वपूर्ण घटनाओं के समय को याद करने में आपको कठिनाई होती है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

5. क्या आपको किताब या अखबार पढ़ते समय ध्यान लगाने में कठिनाई होती है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

6. क्या आपको हाल ही में पढ़ी गई या बताई गई बातों को याद करने में समस्या होती है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

7. क्या आपको लगता है कि जो आप शुरू करते हैं उसे पूरा नहीं करते हैं?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

8. क्या दैनिक/ रोज़मर्रा के कार्यों को पूरा करने में आपको सामान्य से अधिक समय लगता है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

9. क्या आप कभी रास्तों में भटका हुआ महसूस करते है??

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

10. जब लोग आपको किसी बातचीत या आपके द्वारा सुनी गई टिप्पणी की याद दिलाते हैं, तो क्या आपको यह आभास होता है कि आपने इसे पहली बार सुना है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

11. क्या कभी-कभी आपके लिए अपने विचारों को व्यक्त करने के लिए शब्दों को खोजना कठिन होता है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

12. क्या आप ध्यान आसानी से विचलित/ भंग हो जाता है?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

13. क्या आपको सरल मानसिक/ दिमागी हिसाब किताब करने में कठिनाई होती हैं?

0	1	2	3
कभी नहीँ	कभी – कभी	अक्सर	हमेशा

14.क्या आपको यह आभास होता है कि आप बातचीत का अनुसरण नहीं कर सकते?

0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

15.क्या आपने देखा है कि आपको नई जानकारी सीखना मुश्किल लगता है?

0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

16.क्या किसी खास काम में लंबे समय तक एकाग्र रहने के लिए आपको संघर्ष करना पड़ता है?

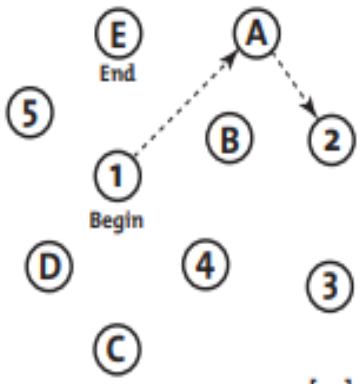
0	1	2	3
कभी नहीँ	कभी - कभी	अक्सर	हमेशा

ANNEXURE 8

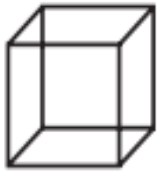
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

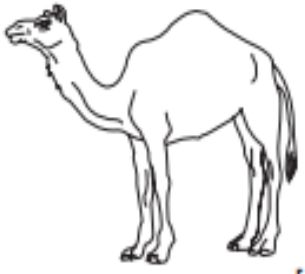
[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING

[ ]

[ ]



[ ]

__/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION — Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

ANNEXURE 9

YOUNG MANIA RATING SCALE (YMRS)

1. **Elevated Mood**
   - 0 [ ] Absent
   - 1 [ ] Mildly or possibly increased on questioning
   - 2 [ ] Definite subjective elevation; optimistic, self-confident; cheerful; appropriate to content
   - 3 [ ] Elevated; inappropriate to content; humorous
   - 4 [ ] Euphoric; inappropriate laughter; singing
2. **Increased Motor Activity-Energy**
   - 0 [ ] Absent
   - 1 [ ] Subjectively increased
   - 2 [ ] Animated; gestures increased
   - 3 [ ] Excessive energy; hyperactive at times; restless (can be calmed)
   - 4 [ ] Motor excitement; continuous hyperactivity (cannot be calmed)
3. **Sexual Interest**
   - 0 [ ] Normal; not increased
   - 1 [ ] Mildly or possibly increased
   - 2 [ ] Definite subjective increase on questioning
   - 3 [ ] Spontaneous sexual content; elaborates on sexual matters; hypersexual by self-report
   - 4 [ ] Overt sexual acts (toward patients, staff, or interviewer)
4. **Sleep**
   - 0 [ ] Reports no decrease in sleep
   - 1 [ ] Sleeping less than normal amount by up to one hour
   - 2 [ ] Sleeping less than normal by more than one hour
   - 3 [ ] Reports decreased need for sleep
   - 4 [ ] Denies need for sleep
5. **Irritability**
   - 0 [ ] Absent
   - 2 [ ] Subjectively increased
   - 4 [ ] Irritable at times during interview; recent episodes of anger or annoyance on ward
   - 6 [ ] Frequently irritable during interview; short, curt throughout
   - 8 [ ] Hostile, uncooperative; interview impossible
6. **Speech (Rate and Amount)**
   - 0 [ ] No increase
   - 2 [ ] Feels talkative
   - 4 [ ] Increased rate or amount at times, verbose at times
   - 6 [ ] Push; consistently increased rate and amount; difficult to interrupt
   - 8 [ ] Pressured; uninterruptible, continuous speech
7. **Language-Thought Disorder**
   - 0 [ ] Absent
   - 1 [ ] Circumstantial; mild distractibility; quick thoughts

2 [ ] Distractible, loses goal of thought; changes topics frequently; racing thoughts
3 [ ] Flight of ideas; tangentiality; difficult to follow; rhyming, echolalia
4 [ ] Incoherent; communication impossible

8. Content

0 [ ] Normal
2 [ ] Questionable plans, new interests
4 [ ] Special project(s); hyper-religious
6 [ ] Grandiose or paranoid ideas; ideas of reference
8 [ ] Delusions; hallucinations

9. Disruptive-Aggressive Behavior

0 [ ] Absent, cooperative
2 [ ] Sarcastic; loud at times, guarded
4 [ ] Demanding; threats on ward
6 [ ] Threatens interviewer; shouting; interview difficult
8 [ ] Assaultive; destructive; interview impossiblE

10. Appearance

0 [ ] Appropriate dress and grooming
1 [ ] Minimally unkempt
2 [ ] Poorly groomed; moderately disheveled; overdressed
3 [ ] Disheveled; partly clothed; garish make-up
4 [ ] Completely unkempt; decorated; bizarre garb

11. Insight

0 [ ] Present; admits illness; agrees with need for treatment
1 [ ] Possibly ill
2 [ ] Admits behavior change, but denies illness
3 [ ] Admits possible change in behavior, but denies illness
4 [ ] Denies any behavior change.

ANNEXURE 10

Hamilton Depression Rating Scale (HAM-D)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

---

1 DEPRESSED MOOD *(sadness, hopeless, helpless, worthless)*

0 |_| Absent.
1 |_| These feeling states indicated only on questioning.
2 |_| These feeling states spontaneously reported verbally.
3 |_| Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.
4 |_| Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2 FEELINGS OF GUILT

0 |_| Absent.
1 |_| Self reproach, feels he/she has let people down.
2 |_| Ideas of guilt or rumination over past errors or sinful deeds.
3 |_| Present illness is a punishment. Delusions of guilt.
4 |_| Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3 SUICIDE

0 |__| Absent.
1 |__| Feels life is not worth living.
2 |_| Wishes he/she were dead or any thoughts of possible death to self.
3 |_| Ideas or gestures of suicide.
4 |__| Attempts at suicide (any serious attempt rate 4).

4 INSOMNIA: EARLY IN THE NIGHT

0 |_| No difficulty falling asleep.
1 |_| Complains of occasional difficulty falling asleep, i.e. more than ½ hour.
2 |_| Complains of nightly difficulty falling asleep.

5 INSOMNIA: MIDDLE OF THE NIGHT

0 |_| No difficulty.
1 |_| Patient complains of being restless and disturbed during the night.
2 |_| Waking during the night – any getting out of bed rates 2 (except for purposes of voiding).

6 INSOMNIA: EARLY HOURS OF THE MORNING

0 |_| No difficulty.
1 |_| Waking in early hours of the morning but goes back to sleep.
2 |__| Unable to fall asleep again if he/she gets out of bed.

7 WORK AND ACTIVITIES

0 |_| No difficulty.
1 |_| Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.
2 |_| Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).
3 |_| Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.
4 |_| Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8 RETARDATION (slowness of thought and speech, impaired ability to concentrate, decreased motor activity)

0 |_| Normal speech and thought.
1 |__| Slight retardation during the interview.
2 |_| Obvious retardation during the interview.
3 |__| Interview difficult.
4 |__| Complete stupor.

9 AGITATION

0 |__| None.
1 |__| Fidgetiness.
2 |__| Playing with hands, hair, etc.
3 |__| Moving about, can't sit still.
4 |__| Hand wringing, nail biting, hair-pulling, biting of lips.

10 ANXIETY PSYCHIC

0 |_| No difficulty.
1 |__| Subjective tension and irritability.
2 |__| Worrying about minor matters.
3 |__| Apprehensive attitude apparent in face or speech.
4 |_| Fears expressed without questioning.

11 ANXIETY SOMATIC (physiological concomitants of anxiety) such as:

gastro-intestinal – dry mouth, wind, indigestion, diarrhea, cramps, belching
cardio-vascular – palpitations, headaches
respiratory – hyperventilation, sighing
urinary frequency
sweating

0 |__| Absent.
1 |__| Mild.
2 |__| Moderate.
3 |__| Severe.
4 |__| Incapacitating.

12 SOMATIC SYMPTOMS GASTRO-INTESTINAL

0 |__| None.
1 |_| Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 |_| Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13 GENERAL SOMATIC SYMPTOMS

0 |__| None.
1 |_| Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
2 |_| Any clear-cut symptom rates 2.

14 GENITAL SYMPTOMS (symptoms such as loss of libido, menstrual disturbances)

0 |__| Absent.
1 |__| Mild.
2 |__| Severe.

15 HYPOCHONDRIASIS

0 |_| Not present.
1 |__| Self-absorption (bodily).
2 |__| Preoccupation with health.
3 |__| Frequent complaints, requests for help, etc.
4 |__| Hypochondriacal delusions.

16* LOSS OF WEIGHT *(RATE EITHER a OR b)

a) According to the patient:	**b) According to weekly measurements:**
0 |__| No weight loss.	0 |_| Less than 1 lb weight loss in week.
1 |__| Probable weight loss associated with present illness.	1 |_| Greater than 1 lb weight loss in week.
2 |_| Definite (according to patient) weight loss.	2 |_| Greater than 2 lb weight loss in week.
3 |__| Not assessed.	3 |_| Not assessed.

17 INSIGHT

0 |_| Acknowledges being depressed and ill.
1 |_| Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 |_| Denies being ill at all.

Total score: |__|__|

This scale is in the public domain.

ANNEXURE 11

WHO-UMC Causality Categories

Certain • Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon) • Rechallenge satisfactory, if necessary
Probable/likely • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible • Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanation
Conditional/unclassified • Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/unclassifiable • Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

ANNEXURE 12

Medication Adherence Rating Scale

MARS questionnaire

	Question	Answer
1	Do you ever forget to take your medication?	Yes / No
2	Are you careless at times about taking your medication?	Yes / No
3	When you feel better, do you sometimes stop taking your medication?	Yes / No
4	Sometimes if you feel worse when you take the medication, do you stop taking it?	Yes / No
5	I take my medication only when I am sick	Yes / No
6	It is unnatural for my mind and body to be controlled by medication	Yes / No
7	My thoughts are clearer on medication	Yes / No
8	By staying on medication, I can prevent getting sick.	Yes / No
9	I feel weird, like a 'zombie' on medication	Yes / No
10	Medication makes me feel tired and sluggish	Yes / No

ANNEXURE 13

Hartwig's Severity Assessment Scale:

NO	TYPEOF ADR	Severity scores 1-7						
		1	2	3	4	5	6	7

Hartwig's severity scale.

- **Level 1**- An ADR occurred but required no change in treatment with the suspected drug

- **Level 2**- The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment was required. No increase in length of stay.

- **Level 3**- The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay.

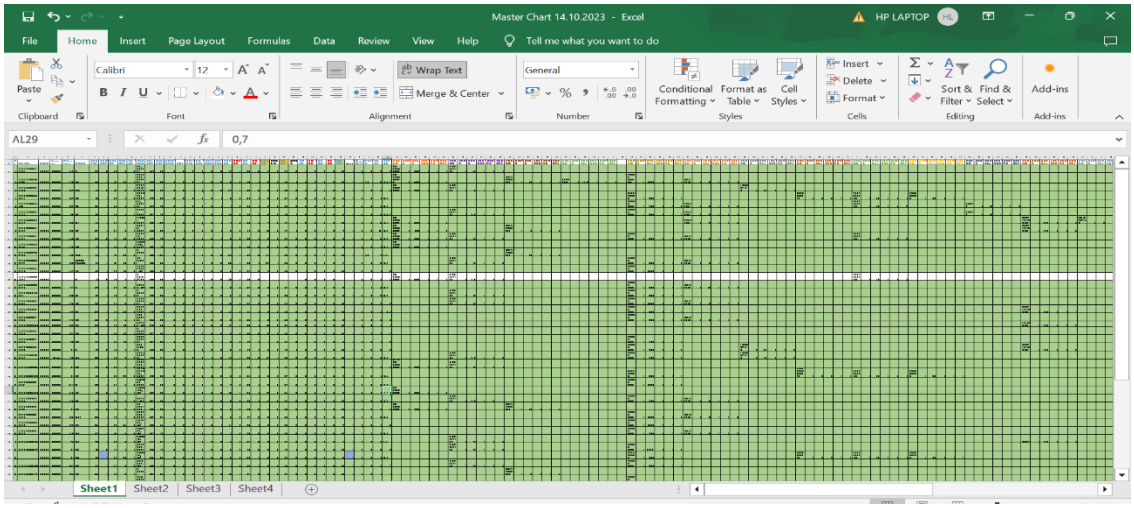
- **Level 4-** Any Level 3 ADR which increases length of stay by at least 1 day or the ADR was the reason for the admission

- **Level 5**- Any Level 4 ADR which requires intensive medical care.

- **Level 6** -The adverse reaction caused permanent harm to the patient.

- **Level 7**- The adverse reaction either directly or indirectly led to the death of the patient.

ANNEXURE 14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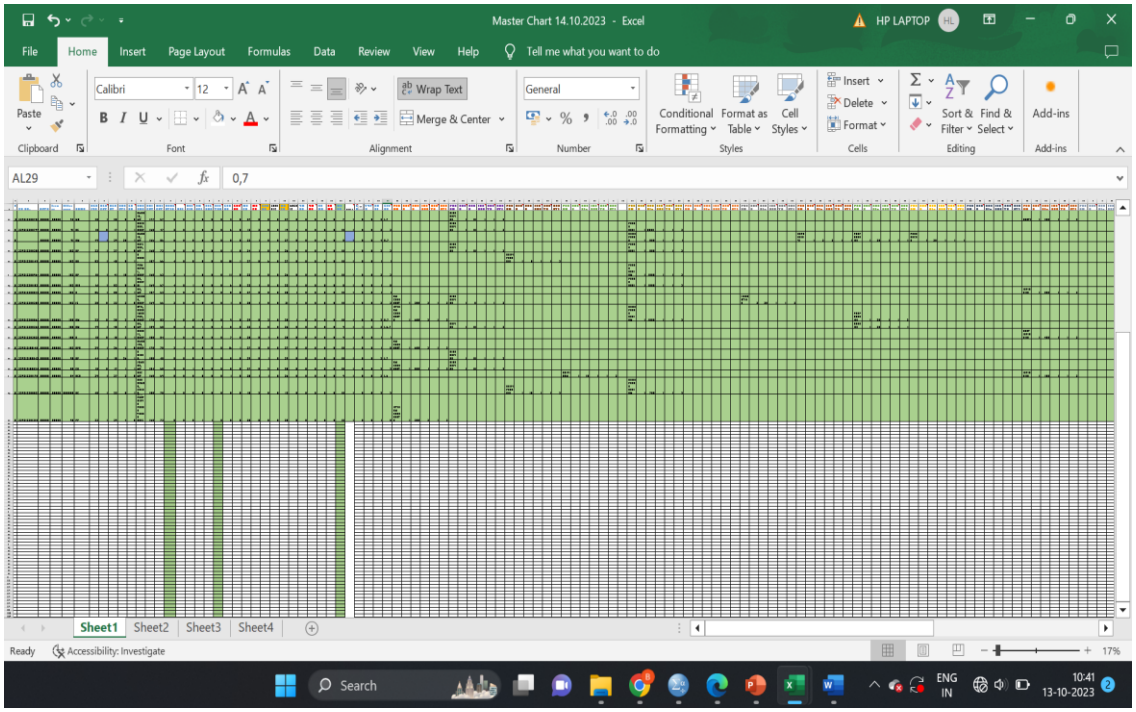
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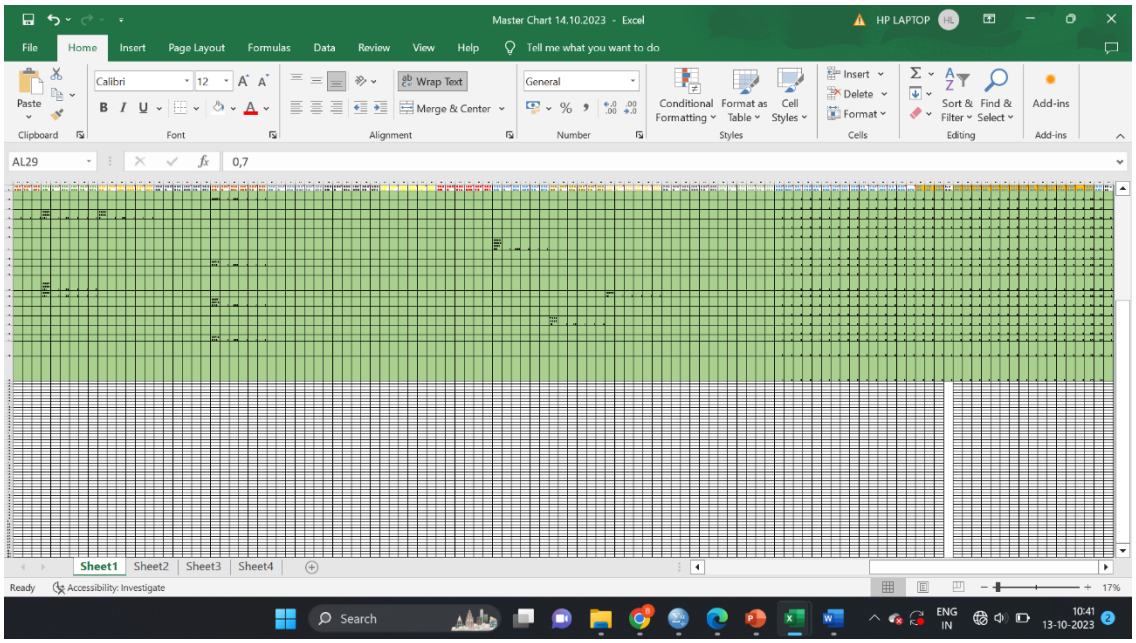
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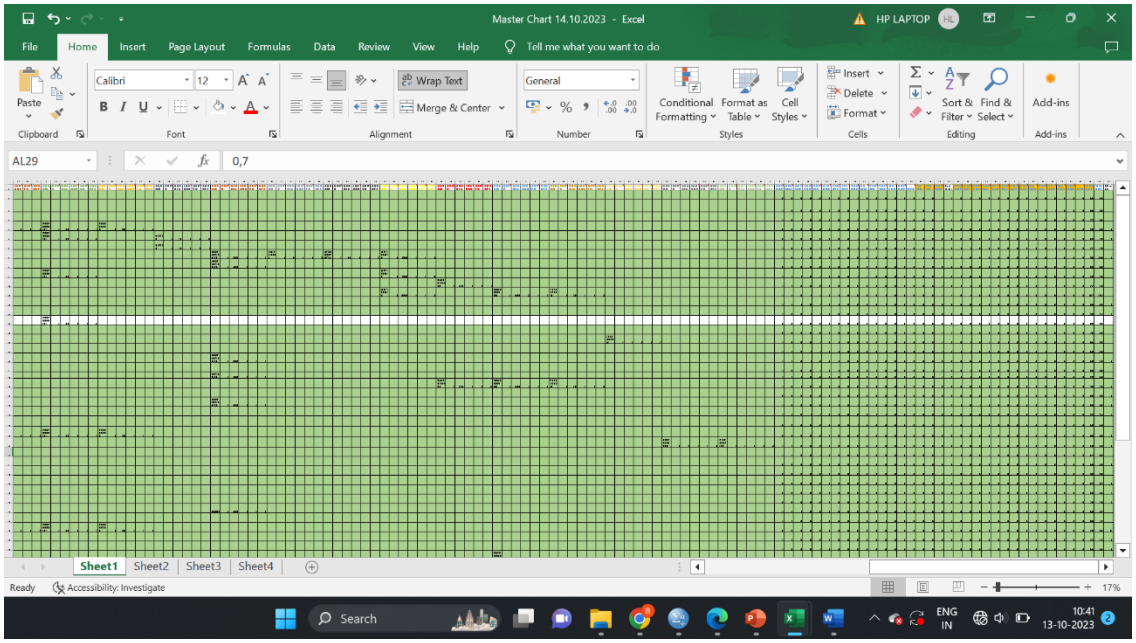
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